Mod Rheumatol (2001) 11:197–204

ORIGINAL ARTICLE

Akiko Mitsuo · Shinichi Aotsuka · Hiroka Iwata
Makiko Kinoshita · Morito Sumiya

Psychiatric dysfunction in connective tissue diseases: association with Sjögren's syndrome

Received: September 1, 2000 / Accepted: January 18, 2001

Abstract We studied 217 patients with connective tissue disease (CTD), comprising 55 patients with primary Sjögren's syndrome (SS), 34 with secondary SS, and 128 without SS. Psychiatric manifestations were investigated using three questionnaires: the Arthritis Impact Measurement Scale 2 (AIMS2), the Cornell Medical Index (CMI), and the Beck Depression Inventory (BDI). Stratified analysis revealed that the frequency of a neurotic state (levels III + IV in CMI) in both primary SS patients (53%; 29% + 24%) and secondary SS patients (67%; 41% + 26%) was significantly greater than in CTD patients without SS (34%; 20% + 14%) ($P < 0.05$ and $P < 0.001$, respectively). The median and Q1–Q3 BDI scores in secondary SS patients (7.5 and 4.0–20.0) were significantly higher than those in CTD patients without SS (5.0 and 1.0–10.0) ($P < 0.05$). Neither the frequency of a neurotic state nor the BDI score differed significantly between patients with primary SS and those with secondary SS. Regression analysis showed significant correlations between the AIMS2 level-of-tension scale and CMI classifications ($rs = 0.676$, $P < 0.001$), and between the AIMS2 mood scale and BDI score ($rs = 0.679$, $P < 0.001$). SS should always be borne in mind when patients with sicca syndrome and multifarious psychiatric complaints are examined.

Key words Arthritis Impact Measurement Scale 2 · Beck Depression Inventory · Cornell Medical Index · Sjögren's syndrome

A Mitsuo · S. Aotsuka (✉)
Division of Clinical Immunology, Clinical Research Institute, International Medical Center of Japan, 1-21-1 Toyama, Shinjuku-ku, Tokyo 162-8655, Japan
Tel. +81-3-3202-7181 (ext. 2816); Fax +81-3-3208-5421
e-mail: Aotsuka@ri.imcj.go.jp

H. Iwata · M. Kinoshita · M. Sumiya
Division of Rheumatology, International Medical Center of Japan, Tokyo, Japan

Introduction

Sjögren's syndrome (SS) is a multisystem autoimmune disorder, and has been estimated to be the second commonest connective tissue disorder after rheumatoid arthritis (RA).[1] It is reported that the syndrome occurs most frequently in middle-aged women, and affects between 2% and 5% of the adult population over 55 years of age.[2] SS has been classified into primary SS, which is not associated with other forms of connective tissue disease (CTD), and secondary SS, in which RA, systemic lupus erythematosus (SLE), or some other autoimmune disorder is present.[3] It is estimated that about half of all cases of SS may be secondary SS, usually associated with RA.[4] However, the prevalence of primary SS in the general population is virtually unknown.[5]

Sjögren's syndrome is a chronic autoimmune exocrinopathy. Its characteristic symptoms, xerophthalmia and xerostomia, result from destructive mononuclear infiltration of the lacrimal and salivary glands, respectively. Recently, medical interest has focused on the variable clinical picture of SS. It has been found that patients exhibit a wide spectrum of extraglandular features that may occur as a result of lymphoid infiltration of the lung, kidney, skin, thyroid gland, stomach, liver, or muscle. Neuropsychiatric involvement in SS patients has increasingly been reported.[6–12] Neurological manifestations include seizure disorders,[13] aseptic meningoencephalitis,[14] symptoms mimicking multiple sclerosis,[9,15] progressive dementia,[10,16] and neuropathy.[12]

The first study of psychiatric manifestations associated with primary SS showed that the commonest psychiatric presentation was a hysteroid-dysphoric state.[8] A subsequent study found that anxiety, depressive moods and personality structure disorders were also psychiatric features of primary SS.[11] Moreover, patients with secondary SS with SLE were reported to have a tendency to develop depressive symptoms.[17] However, there has never been a study comparing psychiatric involvement between patients with primary and secondary SS.

This is the first report to assess and compare psychiatric manifestations in patients with primary and secondary SS.

We used three types of questionnaire administered to three groups of patients: those with primary SS, those with secondary SS, and those with CTD without SS.

Materials and methods

Patients

We randomly selected 274 CTD patients, aged between 15 and 75 years, who were followed at the Division of Rheumatology, International Medical Center of Japan, from January to April 1998. We distributed three types of questionnaire to each patient: the Cornell Medical Index (CMI),[18] the Beck Depression Inventory (BDI),[19] and the Arthritis Impact Measurement Scale 2 (AIMS2).[20] The patients were fully informed and consented to participate. We received 217 returns by hand or mail, giving a response rate of 79%. These included answers from 11 inpatients. The Medical Ethics Committee of the International Medical Center of Japan approved this study.

Table 1 shows the demographic data of the patients from each of the three disease groups (primary SS, secondary SS, and CTD without SS), and the specific diagnosis for each patient with secondary SS and CTD without SS. RA is the most frequent disease associated with both of these groups. A diagnosis of SS was based on the patient fulfilling four of the six diagnostic criteria for SS established by a multicenter European study[21] chart review. Each diagnosis of SLE, RA, or systemic sclerosis (SSc) was made according to the American College of Rheumatology criteria.[22–24] Polymyositis/dermatomyositis (PM/DM) was diagnosed according to Bohan's criteria,[25] and mixed connective tissue disease (MCTD) was diagnosed according to Kasukawa's criteria.[26] The average age of the patients with SLE, RA, SSc, PM/DM, overlap syndrome (OL)/MCTD, and other diseases was 43.4 ± 10.5 years, 59.2 ± 9.8 years, 54.8 ± 11.0 years, 51.0 ± 16.5 years, 49.5 ± 12.4 years, and 53.8 ± 10.9 years (mean ± SD), respectively. In addition, of the 217 study participants, 155 were married (not separated), 23 were divorced or widowed, 29 had never been married, and 10 were of unknown mautal status.

Questionnaires

The CMI is composed of a 144-item somatic symptom questionnaire and a 51-item psychiatric symptom questionnaire.[18] We used a Japanese translation of the CMI,[27–29] in which patients are classified into four levels based on Fukamachi's criteria.[27] Level I represents "diagnosed as normal," level II is "provisionally diagnosed as normal," level III is "provisionally diagnosed as neurotic," and level IV is "diagnosed as neurotic." Levels III and IV are referred to as neurotic states. We adopted the CMI translation because it is widely used for screening people with a tendency to be neurotic, and it has been confirmed that this version is reliable for the Japanese population.[27]

The BDI is one of the most widely used self-administered scales, not only for assessing the intensity of depression in psychiatrically diagnosed patients, but also for detecting depression in normal populations and determining the severity of depressive symptoms. Confidence in this scale has been established for screening people in a depressive state.[19] Subjects are asked to rate 21 items from 0 to 3 according to how they felt at the time. The normal score is 0–13, mild to moderate depression is 14–24, and severe depression is 25–62. We employed the Japanese translation because it is known to be reliable.[30]

The AIMS, published in 1980, was one of the first questionnaires designed specifically for the purpose of assessing health states in subjects with rheumatic disease.[31] The AIMS scale items were later revised, and three new scales were added to evaluate arm function, work, and social support. Sections were also added to assess satisfaction with function, attribution of problems to arthritis, and self-designation of priority regions for improvement. The new instrument, published in 1992, was called AIMS2.[20] We used a Japanese translation whose validity and reliability were reported to be comparable to those of the original.[32] AIMS2 contains 12 scales: mobility, walking and bending, hand and finger function, arm function, self-care, household tasks, social activities, support from family and friends, arthritis pain, work, level of tension, and mood (Table 2). The scores are rated from 0 (worst) to 10 (best). AIMS2 is considered to be an excellent test because it can estimate the physical, social, and psychiatric aspects of the quality of life (QOL) of

Table 1. Demographic data of the patients included in this study, and diagnoses of those with connective tissue diseases (CTD) other than, or in addition to, Sjögren's syndrome (SS)

Groups	Patient number	Men/women	Age (years)		Other CTD: number of patients with					
			Mean ± SD	Median	SLE	RA	SSc	PM/DM	OL/MCTD	Others[a]
Primary SS	55	0/55	61.5 ± 8.4	62	–	–	–	–	–	–
Secondary SS	34	1/33	59.2 ± 7.4	61	8 (24)[b]	15 (44)	5 (15)	3 (9)	3 (9)	0 (0)
CTD without SS	128	25/103	50.1 ± 13.1	51	46 (36)	47 (37)	6 (5)	5 (4)	9 (7)	15 (12)

[a] Others consisted of one patient with polyarteritis nodosa, five patients with Takayasu arteritis, three patients with Behçet's disease, one patient with discoid lupus erythematosus, four patients with polymyalgia rheumatica, and one patient with Wegener granulomatosis

[b] Percentage are given in parentheses

SLE, systemic lupus erythematosus; RA, rheumatoid arthritis; SSc, systemic sclerosis; PM/DM, polymyositis/dermatomyositis; OL, overlap syndrome; MCTD, mixed connective tissue disease

a patient. To confirm the validity of the two psychiatric scales CMI and BDI, whose reliabilities have been confirmed, we investigated the relationships between these and the AIMS2 scale for assessing level of tension and mood.

Statistical analysis

Data are expressed as median and mean ± SD. The data were analyzed with a statistical software package (StatFlex; ViewFlex, Tokyo, Japan), the Mann–Whitney *U*-test, Spearman's rank correlation, the χ^2 test, and multiple regression analysis. Differences at $P < 0.05$ were considered to be statistically significant.

Table 2. Correlation of Cornell Medical Index (CMI) classification grade with AIMS2 scales among all CTD patients by univariate and multivariate regression

	CMI	
	Spearman's correlation coefficient	Multiple correlation coefficient
BDI	0.646***	–
AIMS2 scale		
1 Mobility level	0.544***	0.225**
2 Walking and bending	0.456***	0.070
3 Hand and finger function	0.322***	0.051
4 Arm function	0.340***	−0.121
5 Self-care	0.490***	0.003
6 Household tasks	0.468***	−0.029
7 Social activities	0.236***	−0.004
8 Support from family and friends	0.323***	0.111*
9 Arthritis pain	0.323***	0.012
10 Work	0.527***	0.126*
11 Level of tension	0.676***	–
12 Mood	0.618***	–

* $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$ ($n = 217$)

Results

Stratified analysis

The average age of all the patients was 54.4 ± 12.4 years (mean ± SD). A neurotic state (level III + level IV on the CMI) was observed in 44% (25% + 19%) of patients, and the median (Q1–Q3) BDI score was 6.0 (2.5–11.0). The median (Q1–Q3) AIMS2 level of tension was 2.5 (0.5–4.5), and the median (Q1–Q3) AIMS2 mood scale was 2.0 (1.0–4.0).

The results for each group (primary SS, secondary SS, and CTD without SS) were as follows: a neurotic state (level III + level IV on the CMI) was observed in 53% (29% + 24%) of patients with primary SS, 67% (41% + 26%) of patients with secondary SS, and 34% (20% + 14%) of CTD patients without SS. The frequency of a neurotic state in both primary and secondary SS patients was significantly greater than in CTD patients without SS ($P < 0.05$ and $P < 0.001$ by χ^2 test, respectively; Fig. 1). The frequency of a neurotic state did not differ significantly between patients with primary SS and those with secondary SS.

The median (Q1–Q3) AIMS2 levels of tension were 2.5 (1.0–5.0) in patients with primary SS, 3.8 (1.5–5.0) in patients with secondary SS, and 2.0 (0.5–4.5) in CTD patients without SS. The median level of tension in secondary SS patients was significantly higher than that in CTD patients

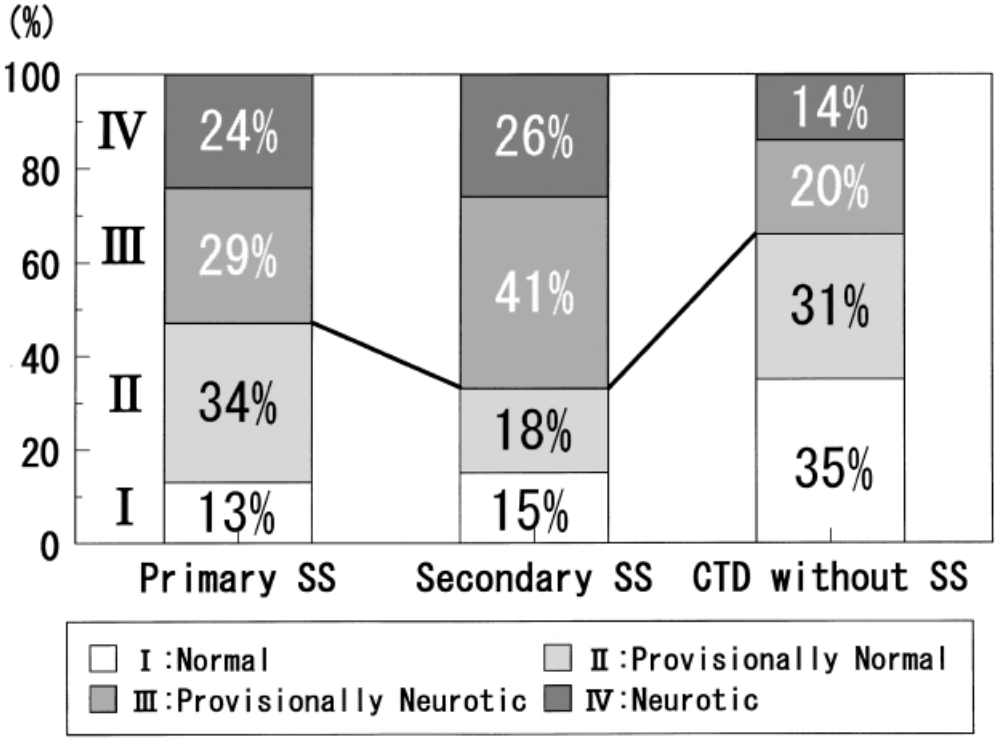

Fig. 1. Cornell Medical Index (CMI) classifications based on Fukamachi's criteria of groups of patients with primary Sjögren's syndrome (SS) ($n = 55$), secondary SS ($n = 34$), and connective tissue disease (CTD) without SS ($n = 128$). Levels III and IV are referred to as neurotic states

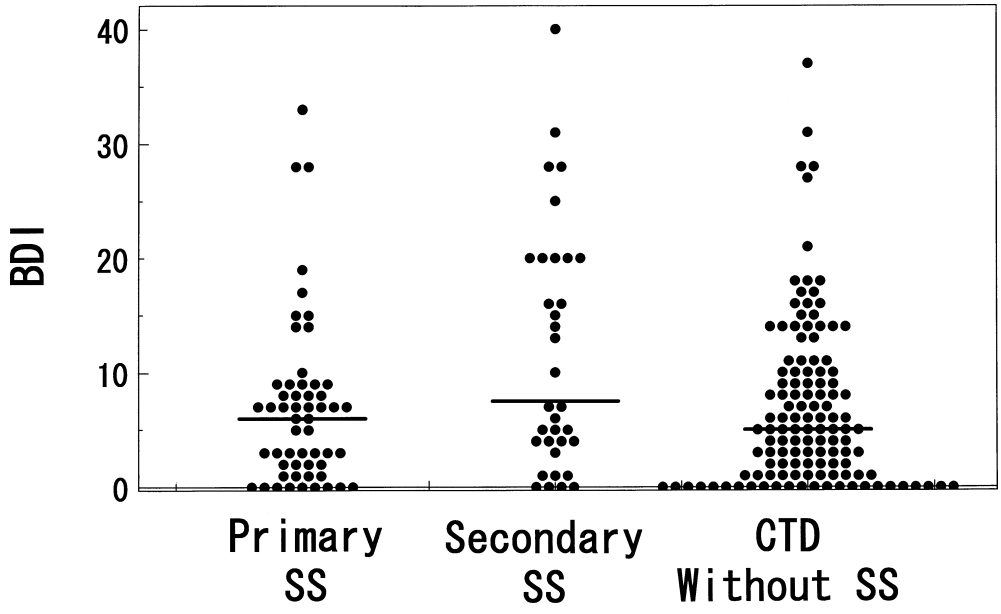

Fig. 2. Beck Depression Inventory (BDI) scores in groups of patients with primary SS (n = 55), secondary SS (n = 34), and CTD without SS (n = 128). *Horizontal bars* indicate the median

without SS ($P < 0.05$ by Mann–Whitney U-test). The median level of tension in primary SS patients was slightly higher than that in CTD patients without SS, but this was not statistically significant.

The median (Q1–Q3) BDI scores were 6.0 (2.3–9.0) in patients with primary SS, 7.5 (4.0–20.0) in patients with secondary SS, and 5.0 (1.0–10.0) in CTD patients without SS. The median BDI score in secondary SS patients was significantly higher than that in CTD patients without SS ($P < 0.05$ by Mann–Whitney U-test; Fig. 2). The score in primary SS patients (6.0 and 2.3–9.0) tended to be higher than that in CTD patients without SS, but this was not statistically significant. The score did not differ significantly between patients with primary SS and those with secondary SS.

The median (Q1–Q3) AIMS2 mood scales were 2.0 (1.0–4.0) in patients with primary SS, 3.7 (0.5–6.3) in patients with secondary SS, and 2.0 (1.0–4.0) in CTD patients without SS. The median mood scale in secondary SS patients was significantly higher than that in CTD patients without SS ($P < 0.05$ by Mann–Whitney U-test).

Univariate and multivariate regression

To assess the usefulness of AIMS2 in evaluating the psychiatric aspects of CTD, we used univariate and multivariate regression analysis within individual CTD patients with CMI classifications, BDI scores, and AIMS2 scales. The AIMS2 level-of-tension scale, which measured the tendency to be in a neurotic state, was positively associated with the CMI classification ($rs = 0.676$, $P < 0.001$ by Spearman's rank correlation test; Table 2, Fig. 3). The AIMS2 mood scale, which measured the tendency to be in a depressive state, was significantly associated with the BDI score ($rs = 0.679$, $P < 0.001$; Table 3, Fig. 4). In addition, the AIMS2 level-of-tension scale was highly correlated with the AIMS2 mood scale ($rs = 0.795$, $P < 0.001$; data not shown).

Table 3. Correlation of Beck Depression Inventory (BDI) scores and AIMS2 scales among all CTD patients by univariate and multivariate regression

	BDI	
	Spearman's correlation coefficient	Multiple correlation coefficient
CMI	0.646***	–
AIMS2		
1 Mobility level	0.488***	0.182*
2 Walking and bending	0.452***	0.065
3 Hand and finger function	0.373***	0.114
4 Arm function	0.377***	0.023
5 Self-care	0.500***	−0.094
6 Household tasks	0.483***	−0.007
7 Social activities	0.305***	0.023
8 Support from family and friends	0.380***	0.177**
9 Arthritis pain	0.255***	−0.039
10 Work	0.474***	0.093
11 Level of tension	0.614***	–
12 Mood	0.679***	–

* $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$ (n = 217)

Multiple regression analysis revealed that the CMI classification was positively associated with scales of mobility level ($P < 0.01$), support from family ($P < 0.05$), and work ($P < 0.05$) (Table 2). The BDI scores were also found to correlate positively with scales of mobility level ($P < 0.05$) and support from family ($P < 0.01$) (Table 3). To eliminate the effects of psychiatric aspects, the level-of-tension and mood scales were excluded from this analysis.

Discussion

In this study, we found that a neurotic state was associated with both primary and secondary SS by the CMI classification. The AIMS2 level-of-tension scale also confirmed the

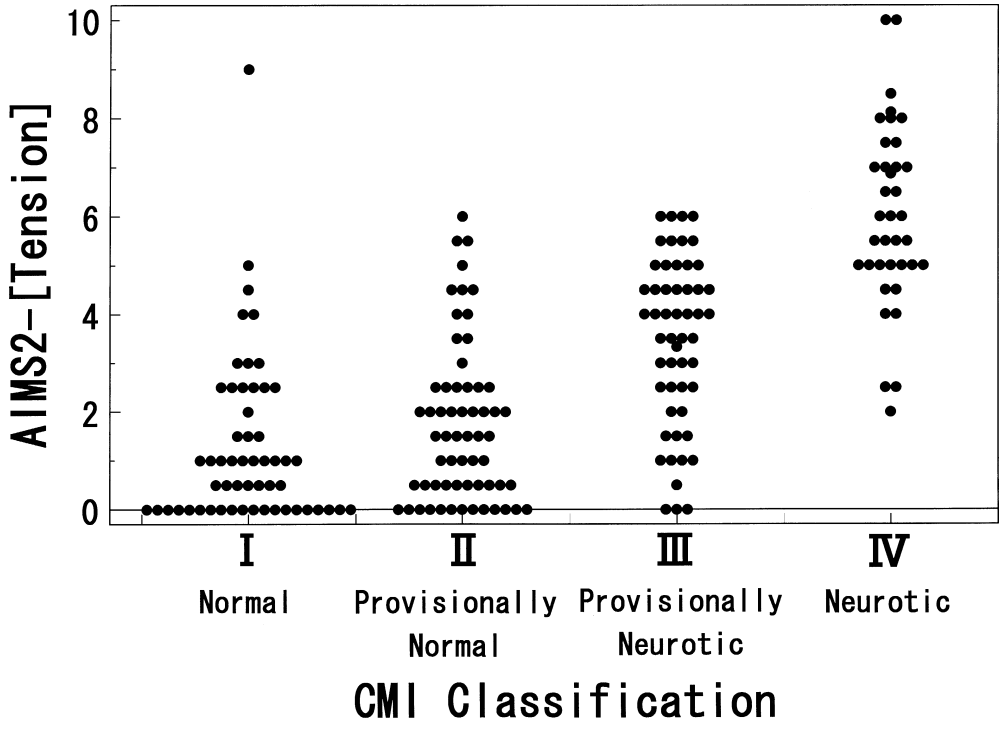

Fig. 3. Association of CMI classification grade based on Fukamachi's criteria and AIMS2 level-of-tension scale among individual CTD patients by Spearman's rank correlation test ($n = 217$, $rs = 0.676$, $P < 0.001$)

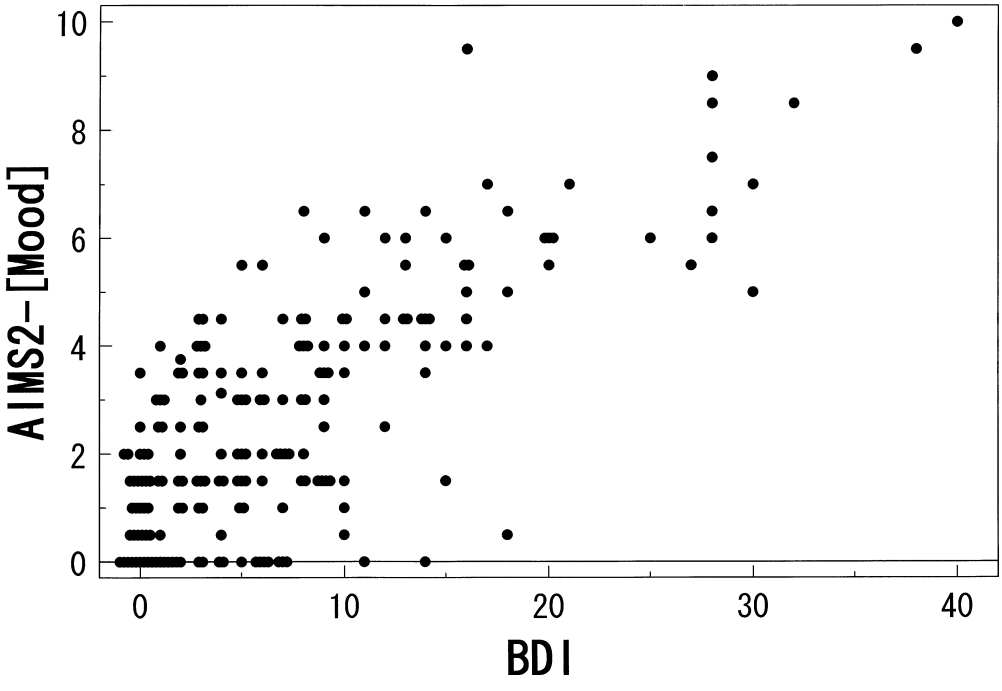

Fig. 4. Association of BDI scores and AIMS2 mood scale among individual CTD patients by Spearman's rank correlation test ($n = 217$, $rs = 0.679$, $P < 0.001$)

correlation of a neurotic state with secondary SS. Furthermore, we demonstrated a connection between a depressive state and secondary SS using both the BDI score and the AIMS2 mood scale.

With regard to the neurotic state of SS patients, there have been several studies of psychiatric symptoms in primary SS patients.[8–12] However, this is the first report to demonstrate an associated neurotic state even in patients with secondary SS. Malinow et al.[8] reported that hysteroid–dysphoric features and concurrent states of severe anxiety, panic, somatization, dissociative episodes, hysterical personality, and cognitive abnormality were frequently seen in patients with primary SS. They considered that these symptoms more closely fulfill the criteria of the American Psychiatric Association's diagnostic and statistical manual (DSM III)[33] for "atypical depression" or "dysthymic disorder" (depressive neurosis), than those of a "major depressive episode" characteristic of bipolar or unipolar disease. Our findings that a neurotic state was associated with primary SS are compatible with theirs.

Unspecified autoimmune derangements associated with sicca syndrome might be linked to the neurotic state of patients with either primary or secondary SS. We also demonstrated the association of a depressive state with secondary SS. Since it was thought that the depressive state of patients with secondary SS might be attributable to psychiatric overloading due to the presence of more than two CTDs, we studied three patients with overlap syndrome (OL). It was found that the three OL patients in this study had BDI scores of 3, 15, and 20. The frequency of a depressive state in SLE patients with SS (63%) was significantly higher than that in SLE patients without SS (22%). In contrast, the frequency of a depressive state in RA patients with SS (33%) was not significantly different from that in RA patients without SS (15%) (data not shown). It is possible that the depressive tendency of patients with secondary SS might result from mental burdens, although more data will be needed before a statistical analysis can be done. Utset et al.[17] pointed out that SLE patients with SS showed depressive symptoms. They suggested that depression might be a manifestation of an autoimmune disease rather than a response to social stress. In another study, Barendregt et al.[34] found a significant positive correlation between depression and dimensions of reduced motivation and mental fatigue in patients with primary SS. They also observed a negative correlation between general fatigue and plasma noradrenaline, suggesting the involvement of subclinical disturbances of the autonomic nervous system. It remains to be clarified whether psychiatric overloading, autoimmune mechanisms, or other factors could result in a depressive state in secondary SS.

In relation to the association between age and depression, Wright et al.[35] reported that younger people with RA were at higher risk of depression than their older counterparts. Nevertheless, in our study, univariate regression showed no association between age and CMI classification, BDI score, the AIMS2 level-of-tension scale, or the AIMS2 mood scale (data not shown). Therefore, we were unable to demonstrate a relationship between age and psychiatric disturbance.

We also investigated whether marital status was associated with mental state. Ward and Leigh.[36] showed that marriage was associated with a lower rate of progression of functional disability in people with RA. In our study, we found that divorced or widowed participants had a significantly higher frequency of neuroticism on CMI than married and unmarried participants ($P < 0.05$ by χ^2 test, data not shown). The median BDI score, AIMS2 level of tension, and AIMS2 mood scales of divorced people were higher than those of married and unmarried people ($P < 0.05$ by Mann–Whitney U-test, data not shown). Nevertheless, the rates of divorce or widowhood among patients with primary SS, secondary SS, and CTDs without SS (13%, 15%, and 9%, respectively) were not significantly different by χ^2 test. We therefore conclude that marital status may not be associated with psychiatric disturbance in SS patients.

Univariate analysis indicated that the AIMS2 level-of-tension scale correlated positively with CMI classifications. Multivariate analysis indicated that AIMS2 items such as mobility level, support from the family, and work also correlated positively with CMI classifications. This indicates that CTD patients who have complaints about mobility or support from family or friends, or experience difficulty with work, housework, or studying, tend to appear neurotic, possibly due to frustration. The AIMS2 level-of-tension scale might be useful for evaluating this tendency in CTD patients.

Univariate analysis indicated that the AIMS2 mood scale was also correlated positively with BDI score. Multivariate analysis indicated that mobility level and support from the family also correlated positively with BDI score. CTD patients who have difficulty in moving and receive less support from family or friends seem to have a tendency to develop a depressive state. This conclusion implies that support from others can prevent CTD patients developing depression. Contrary to previous reports,[17,37] none of our CTD patients who sensed intense arthralgia experienced depression, possibly because of differences in the study populations. The AIMS2 mood scale may also be useful for evaluating this tendency in CTD patients.

Because we used self-administered scales in this study, we diagnosed psychiatric dysfunction in each patient "indirectly." A correct evaluation would require professional psychiatric examination of each patient. However, since many CTD patients may not realize that they have mental illness, they usually consult specialists in internal medicine, rather than psychiatrists, and as a consequence such patients might not be diagnosed as having mental disorders. We therefore consider it meaningful to use self-administered scales for screening, because we can consult skilled psychiatrists if the scales detect patients with psychiatric dysfunction, and the quality of life of the patients may then be improved.

Although SS is the second most common CTD after RA, SS is easy to overlook if the physician does not consider it in differential diagnosis. Various emotional complaints of patients with SS tend to be ignored, because psychiatric disturbance has been less well appreciated as a complication of SS. Thus the diagnosis of SS should always be borne in mind when examining patients with sicca syndrome and multifarious psychiatric complaints.

At this time, the etiology of SS remains unclear. Malinow et al.[8] reported that postmortem examination of patients with SS showed systemic vasculitis with vascular involvement of the peripheral and central nervous system. They suggested that vasculitis in the brain could cause the development of psychiatric manifestations in SS patients and be an extraglandular manifestation of SS. On the other hand, as we describe above, a recent report has found negative correlations between levels of noradrenaline and general fatigue in patients with primary SS.[34] In addition, Johnson et al.[38] found significantly lower ACTH and cortisol levels and higher TSH levels in primary SS patients than in controls. They found hypoactivity of the hypothalamic–pituitary–adrenal axis in these patients. Therefore, it might be hypothesized that disturbances in immune–neuroendocrine mechanisms involving a range of neuroendocrine sub-

stances, such as catecholamines, neurotransmitters, cytokines, and hormones, also play a role in developing psychiatric dysfunction in SS patients.

Recently, medical interest has focused on the problems of the QOL of CTD patients who are prone to recurrence and have long bouts. However, research into the psychiatric aspects of QOL has tended to lag far behind that on other aspects (e.g., physical or social). When working with SS patients, it is important to remove unnecessary anxiety and ameliorate depression in order to improve their QOL. The clinical application of questionnaires could help identify CTD patients who may be helped by psychological intervention. In addition, because the use of questionnaires is relatively cost-effective, further research in this field with improved questionnaires can be expected.

In conclusion, we have revealed a significant association between a neurotic state and both primary and secondary SS, and a significant association between a depressive state and secondary SS. There is a need for further studies of the pathoetiological mechanisms of the resulting psychiatric manifestations and QOL in SS patients.

Acknowledgments We thank Dr. Akira Hashimoto and Dr. Yasuoki Moroi, of the QOL Survey Committee for Rheumatoid Arthritis in the Ministry of Health and Welfare, for providing the Japanese translation of AIMS2. We are also grateful to Masako Okawa-Takatsuji, Michiyo Shimizu, Midori Horibe, and Hiromi Hata for their secretarial help.

References

1. Moutsopoulos HM, Chused TM, Mann DL, Klippel JH, Fauci AS, Frank MM. Sjögren's syndrome (sicca syndrome): current issues. Ann Intern Med 1980;92:212–26.
2. Hochberg MC. Adult and juvenile rheumatoid arthritis: current epidemiologic concepts. Epidemiol Rev 1981;3:27–44.
3. Moutsopoulos HM, Webber BL, Vlagopoulos TP, Chused TM, Decker JL. Differences in the clinical manifestations of sicca syndrome in the presence and absence of rheumatoid arthritis. Am J Med 1979;66:733–6.
4. Moutsopoulos HM, Velthuis PJ, De Wilde PCM, Kater L. Sjögren's syndrome. In: Kater L, Baart Dela Faille E, editors. Multi-systemic autoimmune disease. An integrated approach. Amsterdam: Elsevier; 1995. p. 173–205.
5. Youinou P, Moutsopoulos HM, Pennec YL. Clinical features of Sjögren's syndrome. Curr Opin Rheumatol 1990;2:687–93.
6. Alexander GE, Provost TT, Stevens MB, Alexander EL. Sjögren's syndrome: central nervous system manifestations. Neurology 1981;31:1391–6.
7. Alexander EL, Provost TT, Stevens MB, Alexander GE. Neurologic complications of primary Sjögren's syndrome. Medicine 1982;61:247–57.
8. Malinow KL, Molina R, Gordon B, Selnes OA, Provost TT, Alexander EL. Neuropsychiatric dysfunction in primary Sjögren's syndrome. Ann Intern Med 1985;193:344–9.
9. Alexander EL, Malinow KL, Lijewski JE, Jerdan MS, Provost TT, Alexander GE. Primary Sjögren's syndrome with central nervous disease mimicking multiple sclerosis. Ann Intern Med 1986;104: 323–30.
10. Alexander EL. Central nervous system (CNS) manifestations of primary Sjögren's syndrome: an overview. Scand J Rheumatol 1986; Suppl 61:161–5.
11. Drosos AA, Andonopolos AP, Lagos G, Angelopoulos NV, Moutsopoulos HM. Neuropsychiatric abnormalities in primary Sjögren's syndrome. Clin Exp Rheumatol 1989;207–9.
12. Hietaharju A, Yli-Kerttula U, Häkkinen V, Frey H. Nervous system manifestations in Sjögren's syndrome. Acta Neurol Scand 1990;81:144–52.
13. Alexander EL, Lijewsky JE, Jerdan MS, Alexander GE. Evidence of an immunopathogenic basis for central nervous system disease in primary Sjögren's syndrome. Arthritis Rheum 1986;29:1223–31.
14. Alexander EL, Alexander GE. Aseptic meningoencephalitis in primary Sjögren's syndrome. Neurology 1983;33:593–8.
15. Bansal SK, Sawhney IMS, Chopra JS. Epilepsia partialis continua in Sjögren's syndrome. Epilepsia 1987;28:362–3.
16. Alexander EL, Steven SB, Provost TT, Petronas N, McFarland HF. Magnetic resonance imaging (MRI) in primary Sjögren's syndrome with CNS disease (CNS–SS): new clues to pathogenesis. Arthritis Rheum 1986;29:S63.
17. Utset TO, Golden M, Siberry G, Kiri N, Crum RM, Petri M. Depressive symptoms in patients with systemic lupus erythematosus: association with central nervous system lupus and Sjögren's syndrome. J Rheumatol 1994;21:2039–45.
18. Broadman K, Erdmann AJ, Lorge I, Wolff HG, Broadbent TH. The Cornell Medical Index: an adjunct to medical interview. J Am Med Assoc 1949;140:530–4.
19. Beck AT, Ward CH, Mendelson M, Moch J, Erbaugh J. An inventory for measuring depression. Arch Gen Psychiatry 1961;4:561–71.
20. Meenan RF, Mason JH, Anderson JJ, Guccione AA, Kazis LE. AIMS2: the content and properties of a revised and expanded arthritis impact measurement scales health status questionnaire. Arthritis Rheum 1992;35:1–10.
21. Vitali C, Bombardieri S, Moutsopoulos HM, et al. Preliminary criteria for the classification of Sjögren's syndrome. Result of a prospective concerted action supported by the European Community. Arthritis Rheum 1992;36:340–7.
22. Tan EM, Cohen AS, Fries JF, Masi AT, McShane DJ, Rothfield NF, et al. The 1982 revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum 1982;25:1271–7.
23. Arnett FC, Edwothy SM, Bloch DA, Mcshane DJ, Fries JF, Cooper NS, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum 1988;31:315–24.
24. Subcommittee for scleroderma criteria of the American Committee. Preliminary criteria for the classification of systemic sclerosis. Arthritis Rheum 1980;23:581–90.
25. Bohan A, Peter JB, et al. Polymyositis and dermatomyositis. N Engl J Med 1975;292:344–7, 403–7.
26. Kotajima L, Aotsuka S, Sumiya M, Yokohari R, Tojo T, Kasukawa R. Clinical features of patients with juvenile-onset mixed connective tissue disease: analysis of data collected in a nationwide collaborative study in Japan. J Rheumatol 1996;23:1088–94.
27. Fukamachi K. The study on the Cornell Medical Index (II). A discriminative chart as a screening test of neurotics by CMI. Jpn Fukuoka Med Mag 1959;50:3001–9 [abstract in English].
28. Hashiro M, Okumura M. Anxiety, depression, psychosomatic symptoms and autonomic nervous function in patients with chronic urticaria. J Dermatol Sci 1994;8:129–35.
29. Takano K, Tanaka T, Saito T, and the Committee for the Study Group of Adult GH Deficiency. Psychosocial adjustment in a large cohort of adults with growth hormone deficiency treated with growth hormone in childhood: summary of a questionnaire survey. Acta Paediatr Suppl 1994;399:16–9.
30. Murase S, Kitabatake M, Yamauchi T, Mathé AA. Seasonal mood variation among Japanese residents of Stockholm. Acta Psychiatr Scand 1995;92:51–5.
31. Meenan RF, Gertman PM, Mason JH. Measuring health status in arthritis: the arthritis impact measurement scales. Arthritis Rheum 1980;23:146–52.
32. Sato H, Araki S, Hashimoto A, et al. The validity and reliability of a Japanese version of arthritis impact measurement scales in patients with rheumatoid arthritis. Ryumachi 1995;35:566–74 [abstract in English].
33. American Psychiatric Association. Diagnostic and statistical manual of mental disorders: DSM III. American Psychiatric Association; 1980. p. 241–4.
34. Barendregt PJ, Visser MRM, Smets EMA, et al. Fatigue in primary Sjögren's syndrome. Ann Rheum Dis 1998;57:291–5.

35. Wright GE, Parker JC, Smarr KL, Johnson JC, Hewett JE, Walker SE. Age, depression symptoms, and rheumatoid arthritis. Arthritis Rheum 1998;41:298–305.
36. Ward MM, Leigh JP. Marital state and the progression of functional disability in patients with rheumatoid arthritis. Arthritis Rheum 1993;36:581–8.
37. Büchi S, Sensky T, Allard S, et al. Sense of coherence – a protective factor for depression in rheumatoid arthritis. J Rheumatol 1998;25:869–75.
38. Johnson EO, Vlachoyiannopoulos PG, Skopouli FN, Tzioufas AG, Moutsopoulos HM. Hypofunction of the stress axis in Sjögren's syndrome. J Rheumatol 1998;25:1508–14.