Anxiety and Depressive States in Multiple Chemical Sensitivity

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Tonori, H., Aizawa, Y., Ojima, M., Miyata, M., Ishikawa, S. and Sakabe, K. Anxiety and Depressive States in Multiple Chemical Sensitivity. Tohoku J. Exp. Med., 2001, 193(2), 115-126 — Cases with multiple chemical sensitivity (MCS) frequently present mental symptoms. This study discusses the characteristics of the anxiety and depressive state of MCS by comparing patients of MCS with a gender and age-matched control group. In this investigation, MCS cases were selected among those satisfying the diagnostic criteria of Cullen after ruling out other physical diseases. Patients visiting ophthalmologists with other diseases were designated as the control. Evaluation of the anxiety and depressive state was performed in 48 cases of MCS and 48 controls using the Japanese version of the State-Trait Anxiety Inventory, the Self-rating Depression Scale (SDS), and the Hamilton Rating Scale for Depression. Significantly higher mean values of subjective anxiety and a depressive state were obtained in 18 MCS cases than in 18 controls for the follow-up patients, while no significant difference was observed between MCS and controls of 30 new patients for each group. Therefore, anxiety in MCS is characterized by the continuous high anxiety level. MCS is also characterized by a continuance of depressive state at a “neurotic level” category by SDS. The anxiety scores and depressive levels were highly correlated in MCS and controls at the first and subsequent appearances, except those in the follow-up control cases. In conclusion, both anxiety and a depressive state in MCS remained at high level until the subsequent examination, when those in controls decreased to a normal level. —— multiple chemical sensitivity; anxiety; depressive state; state-trait anxiety inventory; self-rating depression scale
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In 1986, Schottenfeld and Cullen (1986a) first reported a case who complained of a medically unexplained symptom by a mild exposure to a chemical substance such as perfume following an occupational exposure to the chemical substance. In 1987, from the observation of a similar case in the Institute of Occupational Medicine, Yale University, Cullen (1987) proposed multiple chemical sensitivity (MCS). Cullen indicated the following seven criteria for diagnosing MCS: 1) that it is caused by any environment-derived chemical substance; 2) the symptoms are involved in two or more organs; 3) the disease may relapse or remit through reactions to the chemicals assumed causative; 4) the symptoms occur due to exposure to a chemical substance with a different structure; 5) the symptoms appear due to exposure of a detectable but extremely low concentration of chemicals; 6) the threshold of critical exposure is extremely low and 7) no generally-performed test can explain the symptom.

Among symptoms complained by patients of MCS, the mental symptom is the most frequent. In the investigation by Lax and Henneberger (1995), loss of energy, difficulty in concentration, a depressive feeling, memory disturbance and fatigability were listed as the most frequent symptoms among patients of MCS assumed to be occupationally induced, both in the first examination and follow-up surveys. Probably, this is the main reason why the mechanism by which chemical exposure causes MCS has not been proven scientifically (Fiedler et al. 1992; Simon et al. 1993) and because MCS cases complained of a large number of mental symptoms, some researchers think that MCS is a manifestation of former psychiatric disorder such as depression, anxiety, and/or somatization disorders (Brodsky 1983, 1987; Stewart 1983; Scottenfeld and Cullen 1986b; Terr 1986; Black et al. 1990; Simon et al. 1990; Staudenmayer et al. 1993).

They also point out the similarities between MCS and former psychiatric disorder such as post-traumatic stress disorder (Scottenfeld and Cullen 1986b), somatization disorder (Brodsky 1983), and obsessive compulsive personality disorder (Rosenberg et al. 1990). However, no consistent understanding of the etiology or pathology has been obtained and there is no conclusion on whether the etiology is a physical or psychogenic one or a combination of these two. Therefore, it is impossible to conclude whether MCS is identical to psychiatric disorders or not at the present time. But, there is a need to describe the features of psychiatric or psychological state in MCS.

Previous studies (Doty et al. 1988; Simon et al. 1990, 1993) pointed out that MCS had significantly more depressive symptomatology than controls by questionnaires. Brown-DeGagne et al. (1998) evaluated 42 patients of MCS with the Beck Depression Inventory (BDI), to classify the results into subscales related with cognition-affective symptoms and those related with somatic-performance and compared them with outpatients of depression. The patients of MCS tended to complain more of somatic-performance related to subscales than did the cases of depression. From this result, the authors pointed out the necessity of paying attention to the following two possibilities in the judgement of depressive seriousness: the total score of BDI may overestimate the depressive seriousness and the patients of MCS are apt to express symptomatic depression in their physical complaints.

Simon et al. (1993) reported that the patients with chemical sensitivity had greater prevalence of current anxiety and depressive disorder than controls (44% vs. 15%). However, this difference did not appear to precede the onset of chemical sensitivity, and 25% of chemically sensitive patients showed no significant current psychological disturbance.
On the other hand, one study (Selner and Studenmayer 1992) indicated no differences between individuals with MCS and controls with regard to depressive symptomatology. Therefore, we examined whether the patients of MCS had stronger anxiety and depression than those of other diseases among new and follow-up patients.

**SUBJECTS AND METHODS**

**Subjects**

This study was performed on 46 cases of MCS and 46 controls from July 1, 1998 to May 11, 1999. Subjects included those who visited the ophthalmologic outpatient clinic at Kitasato University Hospital for suspected MCS either by themselves or after being introduced from other physicians. The possibility of other diseases was denied and the diagnostic criteria of Cullen were satisfied in the subjects. The diagnosis of MCS was made by doctors other than the evaluators of their mental state. In order not to include the same subjects in both groups of the first and subsequent examinations, the investigated cases upon the first examination were excluded from the subsequent examination.

Those having other diseases upon their first and subsequent visits in the same clinic were designated as the “control.” Gender and age matched patients of the control group were collected by randomly examining those who consented to this investigation after an oral explanation was provided on the purpose and method of investigation and how the obtained data was to be used. The diseases in the control groups were retinal and vitreous body diseases (17.2%), diseases of the crystalline lens (10.3%), palpebral diseases (10.3%), squint and external ophthalmoplegia (10.3%) in the new patients, and retinal and vitreous body diseases (52.9%), diseases of the crystalline lens (11.8%), and palpebral diseases (11.8%) in the follow-up patients.

The average ages and standard deviations of all subjects are shown in Table 1. The mean ages of MCS were 42.6 years (s.d. = 15.4) and those of controls were 42.5 years (s.d. = 15.4). The mean ages showed no significant difference between MCS and controls in all subjects and each group of gender and new or follow-up cases. Also, the mean ages had no statistical difference between the new patients and the follow-up patients in each subject group.

**Methods of investigation and its evaluation for mental states**

The State-Trait Anxiety Inventory (STAI, Japanese version, Sankyobo, Kyoto), a questionnaire anxiety test originally developed by Spielberger (1970), was used for evaluating anxiety. For evaluating depression, the Self-rating Depression Scale (SDS, Japanese version, Sankyobo), a questionnaire depression test originally developed by Zung (1965), and the Hamilton Rating Scale for Depression (HRS, Japanese version) (Hamilton 1960) an interview evaluation of depression for doctors were used.

STAI consisted of state anxiety and trait anxiety tests including 20 questions for each for a total of 40. Each question was rated at 1 to 4 points and the greater the score, the stronger the anxiety was assumed to be. According to the manuals of both state anxiety and trait anxiety tests in the Japanese versions, there were five grades of evaluation criteria. According to the manuals of state-trait anxiety inventory in Japanese versions, there were five grades of evaluation criteria. In the state anxiety test, for males, 22 points or less, 23 to 31 points, 32 to 40 points, 41 to 49 points and 50 points or more were judged “very low,” “low,” “normal,” “high” and “very high,” respectively. For females, 21 points or less, 22 to 30 points, 31 to 41 points, 42 to 50 points and 51 points or more were judged “very low,” “low,” “normal,” “high” and “very high,” respectively. On the other hand, in the trait anxiety test, for males, 23 points or less, 24 to 32 points, 33 to 43 points,
Table 1. Mean and range of age in MCS and the control according to gender

<table>
<thead>
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<th></th>
<th>Subjects</th>
<th>MCS</th>
<th>Control</th>
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<tr>
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<td>$42.6 \pm 15.4$</td>
<td>$42.5 \pm 15.4$</td>
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<td></td>
<td></td>
<td>(17-75)</td>
<td>(16-73)</td>
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<tr>
<td>Men</td>
<td>$n$</td>
<td>16</td>
<td>16</td>
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<tr>
<td></td>
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<td>$38.2 \pm 14.0$</td>
<td>$37.8 \pm 13.5$</td>
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<tr>
<td></td>
<td></td>
<td>(17-72)</td>
<td>(18-70)</td>
</tr>
<tr>
<td>Women</td>
<td>$n$</td>
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<td>32</td>
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<td></td>
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<td>$44.8 \pm 15.8$</td>
<td>$44.8 \pm 16.0$</td>
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<td></td>
<td></td>
<td>(16-75)</td>
<td>(16-73)</td>
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<td></td>
<td>(18-75)</td>
<td>(16-73)</td>
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<td></td>
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<td>$38.8 \pm 14.5$</td>
<td>$38.3 \pm 13.9$</td>
</tr>
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<td></td>
<td></td>
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<td>(20-70)</td>
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<td></td>
<td></td>
<td>$43.3 \pm 15.4$</td>
<td>$43.1 \pm 15.3$</td>
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<td></td>
<td></td>
<td>(18-75)</td>
<td>(16-73)</td>
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<tr>
<td>Follow-up patients</td>
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<td>$44.3 \pm 16.4$</td>
<td>$44.6 \pm 16.7$</td>
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<tr>
<td></td>
<td></td>
<td>(17-72)</td>
<td>(16-72)</td>
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<tr>
<td>Men</td>
<td>$n$</td>
<td>4</td>
<td>4</td>
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<tr>
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<td>$36.3 \pm 14.2$</td>
<td>$36.3 \pm 14.2$</td>
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<td>(18-49)</td>
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<td>$n$</td>
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<td></td>
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<td>(19-72)</td>
<td>(16-72)</td>
</tr>
</tbody>
</table>

Shown by mean (years) ± s.d. ( ); range.

44 to 52 points and 53 points or more were judged “very low,” “low,” “normal,” “high” and “very high,” respectively, and for females, 23 points or less, 24 to 33 points, 34 to 44 points, 45 to 54 points and 54 points or more were judged “very low,” “low,” “normal,” “high” and “very high,” respectively.

SDS consisted of 20 items related to the depressive state and each was rated at 1 to 4 points. Theoretically, 20~80 points are to be scored and the greater the score, the stronger the depression is assumed to be. SDS can also be evaluated by being divided into three groups based on total points. In the Japanese version, 35 (±12) points, 49 (±10) points and 60 (±7) points are defined as the normal level, neurotic level and depressive level, respectively.

Theoretically, HRS indicates a range of 0 to 62 points and the greater the score, the stronger the depression is assumed to be.

Statistical analysis

In the statistical analysis for each criterion, the $t$-test was used for comparisons for average values. Correlation coefficients were used for indicating relationship between the two scores.

RESULTS

Frequencies of anxiety and depressive grades in MCS

Anxiety scores. The added proportions of “high” and “very high” in MCS and controls in the new patients were 76.6%, 70.0%, respective-
Fig. 1. Frequency distribution of grades of state anxiety inventory in MCS and controls. Fig. A is the result of the new patients, and Fig. B is the result of the follow-up patients. □, Control; ■, MCS.

ly. On the other hand, the proportion graded “high” or “very high” state anxiety in MCS tended to be larger than those in controls in the follow-up patients (MCS = 50.0%, controls = 27.8%) with no statistical significance (Fig. 1).

The proportion of “high” or “very high” trait anxiety grades showed the same trends as state anxiety both in the new and follow-up patients (the new patients; MCS = 73.4%, controls = 60.0%, the follow-up patients; MCS = 60.0%, controls = 33.4%) (Fig. 2).

Depression scores. The added proportions from “normal~neurotic level” to “depressive level” in MCS and controls in the new patients were 70.0%, 69.2%, respectively. A comparison in the levels of SDS between MCS and
controls in the new patients indicated that the added proportion of subjects classified as the "normal-neurotic level" or advanced levels, MCS (70.0%) did not differ from those of controls (69.2%). On the other hand, MCS (77.8%) tended to be a larger proportion than the controls (33.4%) in the follow-up patients. The new MCS patients (60.0%) tended to have a higher rations than controls (34.6%) only when the proportions of "neurotic level" or advanced ones were added (Fig. 3).

Average scores in MCS and controls

Anxiety scores. Mean scores of both state and trait anxiety tests in the MCS subjects were significantly higher than those of the controls in
Fig. 3. Frequency distribution of levels of the Self-rating Depression Scale in MCS and controls. Fig. 3A is the result of the new patients, and Fig. 3B is the result of the follow-up patients. □, Control; ■, MCS.

cases of the follow-up patients ($p < 0.05$). By contrast, the mean state and trait anxiety scores showed no statistical difference between MCS and controls in the new patients (Table 2).

Depression scores. The mean scales of both SDS and HRS in the MCS subjects were significantly higher than those of controls in cases of the follow-up patients ($p < 0.01$). However, neither scale in MCS significantly differed from those of controls in the new patients (Table 2).
Table 2. The mean scores of questionnaires in MCS and controls

<table>
<thead>
<tr>
<th></th>
<th>State anxiety inventory</th>
<th>Trait anxiety inventory</th>
<th>Self-rating depression scale</th>
<th>Hamilton rating scale for depression</th>
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</thead>
<tbody>
<tr>
<td>New patients</td>
<td></td>
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<tr>
<td>MCS</td>
<td>50.9 ± 13.6</td>
<td>51.2 ± 11.8</td>
<td>47.4 ± 11.3</td>
<td>12.5 ± 5.9</td>
</tr>
<tr>
<td>Controls</td>
<td>45.7 ± 10.8</td>
<td>46.2 ± 10.9</td>
<td>43.3 ± 10.0</td>
<td>8.5 ± 4.3</td>
</tr>
<tr>
<td>Follow-up patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MCS</td>
<td>45.3 ± 8.9</td>
<td>47.3 ± 8.7</td>
<td>45.1 ± 7.4</td>
<td>10.7 ± 5.0</td>
</tr>
<tr>
<td>Controls</td>
<td>39.1 ± 6.0</td>
<td>39.9 ± 8.2</td>
<td>35.5 ± 7.0</td>
<td>3.1 ± 2.9</td>
</tr>
</tbody>
</table>

Shown by mean ± S.D., n.s.; not significantly different, *p < 0.05, **p < 0.01.
'p < 0.05, ′′p < 0.01; compared with controls at the first visits.

Table 3. The correlation coefficients between two questionnaires in MCS and controls

<table>
<thead>
<tr>
<th></th>
<th>State anxiety inventory and trait anxiety inventory</th>
<th>State anxiety inventory and self-rating depression scale</th>
<th>Trait anxiety inventory and self-rating depression scale</th>
<th>Self-rating depression scale and Hamilton rating scale for depression</th>
</tr>
</thead>
<tbody>
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<td>New patients</td>
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<td></td>
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<tr>
<td>MCS</td>
<td>0.87**</td>
<td>0.70**</td>
<td>0.82**</td>
<td>0.74**</td>
</tr>
<tr>
<td>Controls</td>
<td>0.75**</td>
<td>0.72**</td>
<td>0.81**</td>
<td>0.88**</td>
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<tr>
<td>Follow-up patients</td>
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<td></td>
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<tr>
<td>MCS</td>
<td>0.81**</td>
<td>0.58*</td>
<td>0.57*</td>
<td>0.71**</td>
</tr>
<tr>
<td>Controls</td>
<td>0.64**</td>
<td>0.55*</td>
<td>0.46</td>
<td>0.47</td>
</tr>
</tbody>
</table>

*p < 0.05, **p < 0.01.

Average scores of anxiety and depression in the new and follow-up patients according to MCS or controls

Anxiety scores. In MCS, there was no difference in either state and trait anxiety scores between the new patients and the follow-up patients. In the controls, however, the mean scores of both state and trait anxiety inventories of the new patients were significantly higher than those of the follow-up patients (state anxiety inventory; p < 0.01, trait anxiety inventory; p < 0.05) (Table 3).

Depression scores. In MCS, neither depression score of the new patients differed from those of the follow-up patients. In the controls, the depression scores of the new patients were significantly higher than those of the follow-up control patients (p < 0.01) (Table 2).

The correlation coefficients between the two different scores

Anxiety scores. The two anxiety scores were highly correlated in MCS and controls at first and subsequent appearances (p < 0.01) except for that of the follow-up controls (r = 0.64) (Table 3).

Depression scores. The correlation coefficients between SDS and HRS in MCS and controls was significantly high except for that of the follow-up controls (Table 3).

Relation between anxiety and depression

The correlation coefficients between SDS and state or trait anxiety inventory of the new patients showed a trend of higher values than
those of the follow-up patients. However, there were almost no differences in the correlation coefficients between MCS and controls of both the new patients and the follow-up patients (Table 3).

**DISCUSSION**

**Anxiety of MCS**

From the results of comparison of mean scores for anxiety between MCS and the control, MCS was characterized by higher scores in both state and trait anxiety tests of the follow-up patients compared with the controls. However, the new patients of MCS did not show higher anxiety scores compared with the controls. The categorical classification of state anxiety showed that most frequent grades of anxiety in both MCS and controls were evaluated as “very high” in the new patients and as “normal” categories in the follow-up patients. The largest category of trait anxiety in MCS was “very high” in the new patients and that of controls was “high.” Both MCS and the controls indicated that the most frequent trait category was “normal” in the follow-up cases. MCS had no significant difference in the scores of state and trait anxiety tests between first and subsequent visits, while the control indicated decreased scores of both in the follow-up cases. Therefore, the characteristic of anxiety in MCS is that at the first appearance, the anxiety level is high as controls and remained high at the subsequent visits. On the other hand, the anxiety level in the controls decreased at the subsequent appearance. The finding observed in this study that MCS remained at strong anxiety was similar to a previous study (Simom et al. 1990) when the combined prevalence of either anxiety or depression was very high (prevalence = 95%). This is probably because firstly intensified anxiety is associated with uncertainty about unknown causes and unestablished treatment of MCS and secondarily MCS patients have an inherent trend of anxiety. Spielberger (1970) described that state anxiety was related to subjective emotion of situation-dependent stress or concern and trait anxiety was related to personal character such as a tendency of being anxious or difference in reaction.

Since MCS is characterized by strong anxiety which remained at the follow-up, it is a matter of psychiatric concern whether MCS is identical to the anxiety disorder described in the DSM-IV (Diagnostic and Statistical Manual of Mental Disorders, 4th ed.) of the U.S. Psychiatric Association and Anxiety Disorder listed on ICD-10 of WHO. Some previous studies described the resemblance of MCS to anxiety disorders because the symptoms appeared immediately after an exposure to a very low concentration of chemical substance and recurred under the same or similar conditions. Other articles mentioned the similarity with panic disorders. Kurt (1995) pointed out that MCS was particularly related to a panic or anxiety attack defined in DSM-IV and called MCS “toxic agoraphobia.” Binkley and Kutcher (1997) reported that administrating sodium lactate to all five cases of MCS caused subjective MCS symptoms as opposed to the cases of placebo. Sodium lactate is known as a panic attack-inducing material (Pitts and McClure 1967; Fyer et al. 1984; Cowley and Arana 1990). Based on this finding, they described that there is some bioneurological similarity between MCS and panic disorders. Besides, there are other indications that MCS symptoms may be related to hyperventilation syndrome (Lehrer 1997; Leznoff 1997) and that MCS is a subgroup of somatization disease (Gothe et al. 1995).

Because the present study discusses whether the anxiety of MCS is stronger or not, we could not conclude which of the above-mentioned disorders are similar to MCS in this study. However, as the anxiety of MCS is observed to be higher than controls in the follow-up patients, it seems necessary in the future to examine which anxiety disorder resem-
bles the anxiety of MCS by structural interview. In addition, the mean scores of anxiety inventories in MCS were approximately five points higher than those of controls at first examination though the difference was not significant. Therefore we have to investigate whether MCS has higher anxiety than controls when the numbers of MCS are increased.

**Depressive state of MCS**

Comparing the mean SDS or HRS scores between MCS and the controls, there were no statistical differences in the new patients, while the scores of MCS were higher than those of controls in the follow-up patients. In addition, there was no statistical difference in either scale between the new patients and the follow-up in MCS, whereas the new patients had significantly higher values than the follow-up controls. These findings showed the same trend as anxiety in this study. These suggest that MCS may be characterized by the continuance of depressive state at a “neurotic level” category by SDS. These findings are similar to a previous report that the patients with chemical sensitivity had high prevalence of current anxiety and depressive disorder (44% vs. 15%), however, this difference did not appear to precede the onset of chemical sensitivity (Simon et al. 1993). From these findings, we think that the MCS is characterized by the continuance of some depressive state rather than an advanced degree of the depressive state. The prevalent rates of depression in MCS by use of structured psychiatric interviews (Fiedler et al. 1992; Simon et al. 1993) and by an unstructured one (Stewart and Raskin 1985) were reported to be ranged from 17% to 29%. It may be necessary to assess the depressive state in MCS using controls of psychiatric disorders (i.e., affective disorder, anxiety disorder and personality disorder). We also have to investigate how to change the depressive state in the course of MCS.

The correlation between SDS and HRS in MCS and controls at first and subsequent appearance was high except for that in the follow-up control group. The study on correlation, performed on the depression patients by Prusoff et al. (1972), between questionnaires of the depressive examination and objective evaluations reported that individual symptoms for each item showed a higher correlation during the remitting period after 10 months than the acute period immediately after hospitalization. Another study on the correlation between SDS and HRS, performed on in-patients by Davis et al. (1975), also reported that correlation coefficients on the day, 7th, 14th and 21st days of hospitalization were 0.62, 0.76, 0.72 and 0.95, respectively, suggesting that as the number of days after hospitalization increased, the higher the correlation between SDS and HRS became. These previous findings are not consistent with those of the present MCS study. The characteristics of MCS had almost unchanged correlation coefficients between SDS and HRS in the course of this disease, which may differ from depression. Since MCS is a heterogeneous condition, we should find differences of depressive symptomatology between MCS and psychiatry disorders.

**Relation between anxiety and depressive state in MCS, and controls**

Because of negligible differences of correlation coefficients of anxiety with the depressive state between MCS and controls in both the new patients and the follow-up patients, it is hard to say whether the two scales in MCS are closely correlated.

This study selected patients with ophthalmologic diseases as the controls for the following two reasons: firstly, the investigation on controls can be performed under the same condition as MCS; Secondly, all people seem to have higher anxiety and depressive states due to some disease regardless of its type. Comparison between patients of MCS and those of different diseases can reveal the psychological
states due to MCS.

The control group suffered from various ophthalmologic diseases, but the majority of the affected parts were retinas and corpus vitreum. Especially, for the follow-up patients, the ratio of retinal and corpus vitreum disorders reached 52.9% and some bias may exist due to such a heterogenous composition of diseases.

Acknowledgments

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