

## **The Prognosis After Multidisciplinary Treatment for Patients With Postinfectious Chronic Fatigue Syndrome and Noninfectious Chronic Fatigue Syndrome**

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*Accepted for publication: May 10, 2002*

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*The prognosis after multidisciplinary treatment for patients with postinfectious chronic fatigue syndrome (CFS, n = 9) and noninfectious CFS (n = 9) was clarified. After treatment, natural killer (NK) cell activity increased in the postinfectious CFS group but did not recover to within normal range in the noninfectious CFS group. In the postinfectious CFS group, physical and mental symptoms improved, and 8 patients returned to work. In the noninfectious CFS group, symptoms did not improve, and only 3 patients returned to work. The prognosis of postinfectious CFS group was better than that of noninfectious CFS group. Classification of CFS patients into postinfectious and noninfectious groups is useful for choosing the appropriate treatment in order to obtain better prognosis.*

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**KEY WORDS:** chronic fatigue syndrome; prognosis; multidisciplinary treatment; cognitive-behavioral therapy.

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## INTRODUCTION

Patients with chronic fatigue syndrome (CFS) usually have a poor outcome (Vercoulen *et al.*, 1996a). About 50% of patients with CFS have comorbid major depression (David, 1991). The results from placebo-controlled trials of antidepressants differ; some studies show moderate efficacy (Wearden *et al.*, 1998), whereas others do not (Vercoulen *et al.*, 1996b). Controlled studies suggest that graded exercise therapy (Fulcher and White, 1997) and cognitive-behavioral therapy (Deale *et al.*, 1997) are effective treatments.

The etiology of the CFS is unknown but it is usually considered to be postinfectious or postviral. CFS started with an apparently infectious illness in 72% of cases, while the rest had no apparent infectious onset (Salit, 1997). In this study, patients with CFS were classified into those with infection before the onset of CFS (postinfectious CFS) and those without infection (noninfectious CFS). Multidisciplinary treatment consisting of drug therapy, rehabilitation, counseling, cognitive-behavioral therapy, family therapy, and exercise therapy were performed, and changes in psychobehavioral responses and immunological functions after treatment and prognosis were compared between the two groups.

## METHODS

### Participants

The participants were 18 patients who consulted the medical or psychosomatic clinic of Kagoshima University Hospital, met the CFS diagnostic criteria proposed by the Center for Disease Control (CDC), and were diagnosed based on the criteria recommended in the National Institutes of Health (NIH) conference in 1991 (Schluenderberg *et al.*, 1992). There were 9 patients who developed CFS after definite infection (postinfectious CFS group: age  $30.1 \pm 6.9$ ; 2 single, 7 married, 6 females, 3 males). Two cases each had upper respiratory infection and acute enteritis and one case each had lymphadenitis, tonsillitis, cytomegalovirus infection, Epstein-Barr virus infection, and urinary tract infection. The other 9 patients had no history of infection during the past 3 years (noninfectious CFS group: age  $33.1 \pm 11.0$ ; 4 single, 5 married, 6 females, 3 males). They had stress-associated diseases such as gastric ulcer, hyperventilation syndrome, chronic pancreatitis, or mental disorders such as somatoform disorder, depressive state. Those who had psychiatric disorders such as psychotic disorder, bipolar disorder, and personality disorder before the onset of CFS were excluded. The duration

of illness was longer in the noninfectious CFS group than in the postinfectious CFS group ( $8.2 \pm 3.6$  months vs.  $38.2 \pm 16.4$  months). All patients were treated as inpatients. The control group ( $n = 20$ ) was healthy and had no complaint of chronic fatigue. Results from physical examination, laboratory findings, and chest X-ray studies did not reveal any abnormalities in the control group.

### Procedure

The Cornell Medical Index (CMI) was used to evaluate the neurotic tendency and the presence or absence of autonomic disturbance. CMI is frequently used in the field of Japanese psychosomatic medicine because it facilitates the evaluation of physical findings and mental symptoms. Depression was evaluated using the Self-rating Depression Scale (SDS). This is frequently used at the outpatient clinic because of its answering and scoring simplicity. These tests were done at first consultation and 3 months after treatment.

Changes in immune function after treatment were evaluated in terms of natural killer (NK) cell activity and lymphocyte subsets (proportions of CD4+, CD8+, CD16+, CD56+ cells). Blood was collected at the same time as the psychobehavioral tests were taken.

Prognosis was investigated 2 years after treatment in terms of whether the patient has returned to work and or is still undergoing treatment.

### Multidisciplinary Treatments

CFS patients tend to consider that the cause of their fatigue is not psychological but physical (Hickie *et al.*, 1987). They have many stresses, and their coping behavior for symptoms is inappropriate. Based on these characteristics, our treatment program used both physical and mental approaches; the former aims to decrease physical symptoms, and the latter aims to change cognition and behavior for appropriate coping behavior by making patients realize psychological aspects of CFS.

Multidisciplinary treatment consisting of three-stage treatment programs was carried out for all patients (Table I). Each stage of treatment required 3 weeks. The first stage consisted of drug therapy, rehabilitation, and counseling. The second stage consisted of cognitive-behavioral therapy and family therapy, and the third stage consisted of exercise therapy.

Since psychological approaches in the first stage may cause refusal of treatment, administration of Chinese (herbal) medicine or vitamin C, administration of sedatives, and rehabilitation such as massage and

**Table I.** Flow Chart of Multidisciplinary Treatment

	Drug therapy	Rehabilitation	Counseling	CBT	Family therapy	Exercise
First stage	Chinese medicine Vitamin C Antianxiety Antidepressant	Massage Hotpac Thermotherapy, etc.				
Second stage				Biofeedback Autonomic training		
Third stage						Stretch, Mat Bicycle, Treadmill Walking, etc.
Discharge						

*Note.* CBT: cognitive-behavioral therapy.

thermotherapy were performed to reduce physical fatigue and pain. Mental symptoms such as insomnia, anxiety, hypochondria, and depression were treated using soporifics, antianxiety drugs, and low dose of antidepressants. The dose of these drugs was regulated according to the degree of symptomatic improvements. However, Chinese medicine and vitamin C were continuously administered until discharge from the hospital.

Cognitive-behavioral therapy was initiated after participants gave their consent to our treatment program. Family and developmental history and psychobehavioral responses were investigated. Behavioral problems until the onset of CFS were analyzed. Based on the results, behavioral counseling was performed to promote changes in cognition and behavior. Biofeedback therapy was used to train the patients to recognize and associate a decrease in the skin temperature at the finger tips in hypertense states, i.e., a mind-body correlation. Instructions in autonomic training were given. For family and work problems, family therapy and environmental adjustment were performed to establish emotional and social support systems. The family members and people from office or school were interviewed to promote their understanding of the disease and to ask them for help in CFS treatment.

After decreases in the degrees of fatigue and mental symptoms, exercise therapy was initiated. Exercise was used for stepwise recovery of physical function and systematic desensitization of anxiety for the body in actual scenes. The intensity of exercise was gradually increased from aerobic exercises consisting of stretching and mat exercise to cycling and running on the treadmill, followed by walking and overnight-stay training outside the hospital before discharge.

### Data Analyses

The results were expressed as mean  $\pm$  SD. Data between the two groups were compared with one-way analysis of variance, and  $p$  values  $<0.05$  were considered significant. When significant differences were indicated, Bonferroni's test was used to test for the mean differences between the two groups. Chi-square ( $\chi^2$ ) test was used for the comparison of the prognosis between the two groups, and  $p$  values  $<0.05$  were considered significant.

## RESULTS

### Changes in Psychobehavioral Responses

After treatment, the postinfectious CFS group showed a significant decrease in physical symptoms (Table II), a slight decrease in mental symptoms,

**Table II.** Changes in Psychobehavioral Responses Before and After Treatment

	Control ( <i>n</i> = 20)	Postinfectious CFS ( <i>n</i> = 9)		Noninfectious CFS ( <i>n</i> = 9)	
		Before	After	Before	After
<i>CMI</i>					
Physical complaint	24.2 ± 9.0	43.6 ± 21.4*	25.1 ± 11.4 <sup>†</sup>	59.4 ± 12.0***	46.9 ± 17.7
Fatigue	1.2 ± 1.2	3.9 ± 1.8**	2.7 ± 1.6	4.3 ± 1.3***	4.4 ± 1.5***
Mental complaint	3.8 ± 2.9	14.3 ± 11.7*	7.6 ± 8.6	14.3 ± 4.7*	10.1 ± 3.5
Maladjustment	0.3 ± 0.5	2.9 ± 2.6*	1.6 ± 1.3	4.0 ± 2.4***	2.7 ± 2.2**
Depression	0.1 ± 0.3	1.6 ± 2.3	0.9 ± 2.3	2.0 ± 1.9*	1.1 ± 1.3
Anxiety	0.6 ± 0.9	2.0 ± 1.5*	0.7 ± 0.9	2.1 ± 1.1*	1.3 ± 1.1
Hypersensitivity	0.8 ± 0.8	2.1 ± 1.9	1.1 ± 1.2	1.6 ± 0.8	1.1 ± 0.9
Anger	1.2 ± 1.9	3.0 ± 2.5	1.7 ± 2.4	1.9 ± 1.1	1.7 ± 1.3
Hypertension	0.2 ± 0.4	3.6 ± 3.7**	1.4 ± 2.1	2.4 ± 2.1	2.1 ± 1.6*
<i>SDS</i>	39.8 ± 4.2	48.4 ± 7.3*	38.9 ± 2.0 <sup>‡</sup>	52.3 ± 8.4**	50.7 ± 9.3**

Note. \*  $p < 0.05$ , \*\*  $p < 0.01$ , \*\*\*  $p < 0.001$ ; compared with control; <sup>†</sup>  $p < 0.05$ , <sup>‡</sup>  $p < 0.01$ ; compared with before treatment.

and a significant decrease in the incidence of disease. In addition, fatigue, maladjustment, anxiety, and tension decreased to the control level. SDS values were significantly decreased compared with the pretreatment score.

In the noninfectious CFS group, no significant improvement was observed in either physical or mental symptoms. Both the degree of fatigue and the incidence of disease remained high. Among mental symptoms, anxiety and depression after treatment did not significantly differ from those in the controls, but maladjustment and tension were still marked. SDS values were also high after treatment.

### Changes in Immune Functions

In the postinfectious CFS group, NK cell activity and the proportions of CD16+ and CD56+ cells significantly recovered to within normal range after treatment (Table III). In the noninfectious CFS group, the NK cell activity after treatment was significantly higher than that before treatment but it was still low compared with that for the control. No significant changes were observed after treatment in the leukocyte count, CD3+, CD4+, or CD8+ cell ratio, or lymphocyte proliferations in both CFS groups.

### Prognosis

In the postinfectious CFS group, 8 patients returned to work, and 5 of them changed occupation or workplace; 1 patient is still being treated (Table IV). In the noninfectious CFS group, only 3 patients returned to work but they sometimes consult our hospital because of incomplete improvement of symptoms. The 6 patients who are still under treatment have various physical and mental complaints and they cannot return to work.

## DISCUSSION

Concerning treatment of CFS, antiviral therapy with acyclovir or interferon was reported to be ineffective (Straus *et al.*, 1988). In patients with CFS, a deficiency of essential fatty acids (Behan *et al.*, 1990), immunoglobulin IgG1 subclass (Ganty and Holmes, 1989), or trace elements such as magnesium (Cox *et al.*, 1991) was reported. However, therapy with fatty acids, immunoglobulin, and magnesium was also found to be ineffective (David, 1993). On the other hand, in CFS patients, sleep disorders were often observed, and antidepressants (especially tricyclic drugs) were considered to be

**Table III.** Changes in Immunological Functions Before and After Treatment

	Control ( <i>n</i> = 20)	Postinfectious CFS ( <i>n</i> = 9)		Noninfectious CFS ( <i>n</i> = 9)	
		Before	After	Before	After
NK activity					
E/T					
10:1	25.2 ± 10.7	6.8 ± 3.1***	20.5 ± 9.0‡	3.8 ± 2.0***	10.1 ± 6.8**, †
20:1	35.2 ± 13.4	11.5 ± 3.7**	31.3 ± 14.1‡	6.3 ± 3.2***	14.9 ± 12.3**
Subsets					
CD4+	38.8 ± 9.2	42.6 ± 8.3	31.4 ± 5.0	39.2 ± 5.7	38.9 ± 4.7
CD8+	29.7 ± 7.7	33.0 ± 9.8	36.7 ± 10.9	34.6 ± 4.3	33.9 ± 7.7
CD3+	66.9 ± 9.5	73.0 ± 8.8	65.1 ± 11.8	76.3 ± 8.6	75.0 ± 5.7
CD16+	15.2 ± 6.7	8.0 ± 5.4*	20.3 ± 8.2‡	9.4 ± 6.4	13.1 ± 5.8
CD56+	22.2 ± 7.3	11.1 ± 3.5*	23.5 ± 10.6‡	14.9 ± 8.0	15.8 ± 7.9

Note. \*  $p < 0.05$ , \*\*  $p < 0.01$ , \*\*\*  $p < 0.001$ ; compared with control; †  $p < 0.05$ , ‡  $p < 0.01$ ; compared with before treatment.

**Table IV.** Prognosis of the Two CFS Groups After Treatment ( $\chi^2$  Test)

	Postinfectious CFS ( <i>n</i> = 9)	Noninfectious CFS ( <i>n</i> = 9)	<i>p</i>
Return to work	8	3	<0.05
Treated as outpatients	1	6	

useful (Goldenberg *et al.*, 1986). At present, there is no effective treatment for CFS, and symptomatic therapy is primarily performed.

Cognitive-behavioral therapy can be helpful both in medically unexplained physical symptoms (Sharpe *et al.*, 1992) and in disabling physical diseases (O'Leary *et al.*, 1988). Cognitive-behavioral therapy is an effective and well-established treatment for chronic pain syndromes, depression, anxiety, and panic disorder (Hawton *et al.*, 1989).

We performed multidisciplinary treatment consisting of drug therapy, rehabilitation, counseling, cognitive-behavioral therapy, family therapy, and exercise therapy. From the psychological aspect, both physical and mental symptoms decreased in the postinfectious CFS group, but no improvement was observed and maladjustment, tension, and depression persisted in the noninfectious CFS group. Concerning immune function, NK cell activity and the proportions of CD16+ and CD56+ cells returned to normal after treatment in the postinfectious CFS group. In the noninfectious CFS group, NK cell activity improved but not to the normal level. NK cell activity was reported to decrease due to fatigue (Masuda *et al.*, 1995) and depression (Irwin and Gillin, 1987). In the noninfectious CFS, since no improvement was observed in mental symptoms such as fatigue and depression, recovery of NK cell activity may be delayed.

Concerning prognosis, a study showed improvement in 65 (63%) of 103 patients after symptomatic therapy, but complete disappearance of symptoms was observed only in 3, suggesting a poor prognosis in the presence of primary psychiatric disorders and when patients believed that their symptoms are due to physical diseases (Wilson *et al.*, 1994). Another study showed improvement and resumption of work in 22 (69%) of 32 patients treated by cognitive-behavioral therapy (Butler *et al.*, 1991). Using our treatment program, 8 of the 9 patients in the postinfectious CFS group have returned to work. In this group, organic disorders were eliminated; our multidisciplinary treatment resulted in changes in cognition and behavior and improvement in symptoms. In the noninfectious CFS group only 3 patients have returned to work. This group had problems in family and developmental history, chronic stresses, and long duration of illness. Chronic stress was improved in 3 patients who could return to work because their family and fellow workers

understood the disease and its treatment. However, chronic stress was not relieved in the remaining 6 patients because their family and fellow workers did not help or sufficiently support these patients. Therefore, it was found that a better prognosis can be obtained even in patients with noninfectious CFS group when chronic stress is relieved by the establishment of a support system based on the understanding of the disease, and assistance in CFS treatment by family and fellow workers.

Postinfectious CFS and noninfectious CFS differed in the process until onset, which affected the treatment course and prognosis. The prognosis of CFS is difficult to predict, although cases occurring as part of clusters appear to have a better prognosis as a group than sporadic cases, and those with an acute onset have a better prognosis than those with gradual onset (Levine, 1997). Our postinfectious CFS group was equal to the acute onset group and had a better prognosis. Gradual onset group was equal to noninfectious CFS and this group had a worse prognosis. Therefore, appropriate treatment methods for each group should be used. Our current regimen is highly effective for patients with postinfectious CFS. However, in noninfectious CFS patients, additional therapy that will address the underlying psychological disturbance, training in stress coping and building of emotional and social support systems, obtaining their content to the disease and its treatment by family and fellow workers, and long-sustained efforts may be necessary to obtain better prognosis.

## REFERENCES

- Behan, P. O., Behan, W. M. H., and Horrobin, D. F. (1990). The use of essential fatty acids in chronic fatigue syndrome. *Acta Neurol. Scand.* 82: 209–216.
- Butler, S., Chalder, T., Ron, M., and Wessely, S. (1991). Cognitive behaviour therapy in chronic fatigue syndrome. *J. Neurol. Neurosurg. Psychiatry* 54: 153–158.
- Cox, I. M., Campbell, M. J., and Dowson, D. (1991). Red blood cell magnesium and chronic fatigue syndrome. *Lancet* 337: 757–760.
- David, A. S. (1991). Postviral fatigue syndrome and psychiatry. *Brit. Med. Bull.* 47: 966–988.
- David, R. M. (1993). Pharmacological approaches to the therapy of chronic fatigue syndrome. *Ciba Found. Sympo.* 173: 280–287.
- Deale, A., Chalder, T., Marks, I., and Wessely, S. (1997). A randomised controlled trial of cognitive behavior versus relaxation therapy for chronic fatigue syndrome. *Am. J. Psychiatry* 154: 408–414.
- Fulcher, K. Y., and White, P. D. (1997). Randomised controlled trial of graded exercise in patients with the chronic fatigue syndrome. *BMJ* 314: 1647–1652.
- Ganty, N. M., and Holmes, G. P. (1989). Treatment of patients with chronic fatigue syndrome. *Drugs* 38: 855–862.
- Goldenberg, D. L., Felson, D. T., and Dinerman, H. (1986). A randomized controlled trial of amitriptyline and naproxen in the treatment of patients with fibromyalgia. *Arthritis Rheum.* 29: 1371–1377.

- Hawton, K. E., Salkovskis, P. M., Kirk, J., and Clark, D. M. (1989). *Cognitive Behaviour Therapy for Psychiatric Problems: A Practical Guide*, Oxford Medical Publications, Oxford University Press, London.
- Hickie, I., Lloyd, A., Wakefield, D., and Parker, G. (1987). The psychiatric status of patients with chronic fatigue syndrome. *Br. J. Psychiatry* 156: 534–540.
- Irwin, M., and Gillin, J. C. (1987). Impaired natural killer cell activity among depressive patients. *Psychiatry Res.* 20: 181–182.
- Levine, P. H. (1997). Epidemiologic advances in chronic fatigue syndrome. *J. Psychiatr. Res.* 31: 7–18.
- Masuda, A., Nozoe, S., Naruo, T., Soejima, Y., Nagai, N., Koga, Y., and Tanaka, H. (1995). Natural killer cell activity in relation to psychobehavioral responses, stress coping behavior, and fatigue in healthy adult men. *Jpn. J. Psychosom. Med.* 35: 383–390.
- O’Leary, A., Shoor, S., Lorig, K., and Holman, H. R. (1988). A cognitive–behavioral treatment for rheumatoid arthritis. *Health Psychol.* 7: 527–544.
- Salit, I. E. (1997). Precipitating factors for the chronic fatigue syndrome. *J. Psychiatr. Res.* 31: 59–65.
- Schluenderberg, A., Straus, S. E., Peterson, P., Blumenthal, S., Komaroff, A. L., Spring, S. B., Landy, A., and Buchwald, D. (1992). Chronic fatigue syndrome research—Definition and medical outcome assessment. *Ann. Intern. Med.* 117: 325–331.
- Sharpe, M. C., Povelor, R., and Mayou, R. (1992). Psychological treatment of functional somatic symptoms: A practical guide. *J. Psychosom. Res.* 36: 515–527.
- Straus, S. E., Dale, J. K., Tobi, M., Lawley, T., Preble, O., Blaese, R. M., Hallahan, C., and Henle, W. (1988). Acyclovir treatment of the chronic fatigue syndrome: Lack of efficacy in a placebo-controlled trial. *N. Engl. J. Med.* 319: 1692–1698.
- Vercoulen, J., Swanink, C., Fennis, J., Galama, J., Meer, J., and Bleijenberg, G. (1996a). Prognosis in chronic fatigue syndrome: A prospective study on the natural course. *J. Neurol. Neurosurg. Psychiatry* 60: 489–494.
- Vercoulen, J., Swanink, C., Zitman, F., Vreden, S., Hoofs, M., Fennis, J., Galama, J., Meer, J., and Bleijenberg, G. (1996b). Randomized, double-blind, placebo-controlled study of fluoxetine in chronic fatigue syndrome. *Lancet* 347: 858–861.
- Wearden, A., Morriss, R., Mullis, R., Strickland, P. L., Pearson, D. J., Appleby, L., Campbell, I. T., and Morris, J. A. (1998). Randomized, double-blind, placebo-controlled treatment trial of fluoxetine and graded exercise for chronic fatigue syndrome. *Br. J. Psychiatry* 172: 485–490.
- Wilson, A., Hickie, I., Lloyd, A., and Wakefield, D. (1994). The treatment of chronic fatigue syndrome: Science and Speculation. *Am. J. Med.* 96: 544–550.