Psychosocial Stress, Personality, and the Severity of Chronic Hepatitis C

JUN NAGANO, M.D., SHOJI NAGASE, M.D.
NOBUYUKI SUDO, M.D., CHIHARU KUBO, M.D.

This cross-sectional study examined the association between the severity of chronic hepatitis C and the type 1 personality, which has been shown by Grossarth-Maticek to be strongly related to the incidence of cancer and mortality. Sixty-nine patients with chronic hepatitis C completed the Stress Inventory, a self-report questionnaire to measure psychosocial stress and personality, and were classified into three groups according to hepatitis severity: group A, chronic hepatitis C with a normal serum alanine aminotransferase level; group B, chronic hepatitis C with an elevated alanine aminotransferase level; and group C, liver cirrhosis. Each of four scales related to the type 1 personality—low sense of control, object dependence of loss, unfulfilled need for acceptance, and altruism—was significantly and positively associated with hepatitis severity. The type 1 score, calculated as the average of these scales, was also strongly related to hepatitis severity ($p<0.0001$), and adjustment for age, sex, education level, smoking, drinking, and duration brought no attenuation into the association. Chronic psychosocial stress relevant to the type 1 personality may also influence the course of chronic hepatitis C.

(Psychosomatics 2004; 45:100–106)

An estimated 3% of the world population is chronically infected with the hepatitis C virus. It accounts for approximately 20% of the cases of acute hepatitis and 70% of the cases of chronic hepatitis.[1] In Japan, 2.3 million people are thought to have been infected with the hepatitis C virus, and the majority of liver cirrhosis is related to chronic hepatitis C virus infection.[2] The severity of liver disease related to the hepatitis C virus is extremely variable. While 20%–30% of chronically infected people continue to have minimal liver injury with normal serum alanine aminotransferase levels for decades, the remaining 70%–80% develop chronic hepatitis with elevated alanine aminotransferase levels, of whom 20% or more progress to cirrhosis over 20 to 30 years.[1,2] The only available treatment for elimination of the hepatitis C virus is interferon therapy, but its efficacy so far remains limited.[3] For patients in whom hepatitis progresses, hepatocellular carcinoma is the leading life-threatening complication. Generally, hepatocellular carcinoma occurs in patients with severe fibrosis and inflammation, especially in those with cirrhosis.[1] Virological factors, such as the hepatitis C virus genotype and the serum hepatitis C virus RNA level, do not seem to be associated with the severity of hepatitis or progression to advanced stages.[1,2] This suggests that particular immunological factors of the host play a major role in determining the severity of hepatitis C and, in turn, hepatocarcinogenesis.

Accumulating evidence has linked psychosocial factors to the onset, course, and outcome of chronic and latent viral infections, such as genital herpes virus,[4,5] varicella-

Received Nov. 23, 2002; revision received April 14, 2003; accepted April 28, 2003. From the Institute of Health Science, the Health Care Administration and Management Division, and the Department of Psychosomatic Medicine, Graduate School of Medical Sciences, Kyushu University; and the Department of Internal Medicine, Fukuoka-Higashi National Hospital, Japan. Address reprint requests to Dr. Nagano, Institute of Health Science, Kyushu University, 6-1 Kasuga Park, Kasuga, Fukuoka 816-8580, Japan; nagano@ihs.kyushu-u.ac.jp (e-mail).

zoster virus,[6,7] and human immunodeficiency virus.[8–11] However, little is known about the role of psychosocial factors in the course of chronic hepatitis C virus infection. Epidemiological studies suggest that some psychosocial factors are associated with an increased risk of cancer and mortality.[12,13] Grossarth-Maticek and colleagues[14,15] have shown that their type 1 personality is positively and strongly associated with cancer risk. The type 1 personality is a type characterized by "object dependence,"[14] i.e., a tendency to have highly valued objects (persons or conditions) by which one's emotional status is greatly and chronically swayed, as well as by a tendency to react to stressors with hopelessness and depression. Additional characteristics of the type 1 personality include marked repression of emotions and altruistic behaviors in interpersonal relationships. Since chronic psychosocial stress may affect the severity and progression of chronic hepatitis C and since the severity of hepatitis is regarded as a crucial factor in the hepatocarcinogenesis related to hepatitis C virus, we hypothesized that the type 1 personality would be positively associated with the severity of chronic hepatitis C.

Psychosocial stress can be considered a product of a stressor and the human response to it, a response that includes emotional reactions, cognitive appraisals, behavioral copings, and the use of social supports. When a person responds to stressors in a relatively *stable* manner, such a response pattern can be regarded as an aspect of personality. A person with a personality that easily leads to a certain type of *chronic* stress would have a greater possibility of experiencing such chronic stress. Thus, personality (as a response to stressors) and chronic stress can be difficult to separate, especially when it is assessed by means of a self-report. The Stress Inventory was developed to assess possible disease-prone personalities, as described, as well as chronic psychosocial stresses, including scales related to the type 1 personality.[16,17] In a series of 69 chronically ill hepatitis C patients, we used the Stress Inventory in a cross-sectional study to test this hypothesis.

METHOD

Subjects

Our subjects were outpatients with chronic hepatitis C at the hepatology clinic of a national hospital located in a suburb of Fukuoka City, Japan. Diagnoses of chronic hepatitis C were based on clinical, biochemical, virological, and histological findings. Criteria for recruitment were 1) age under 70 years; 2) no decompensated cirrhosis symptoms, such as intractable ascites, variceal bleeding, or encephalopathy; 3) no hepatocellular carcinoma; 4) no history of other malignant diseases, coronary heart disease, or stroke; 5) no other medical conditions because of which one cannot complete a self-administered questionnaire without assistance; 6) no co-infection with hepatitis B virus; and 7) no interferon treatment within the past 6 months. Patients who had succeeded in eliminating hepatitis C virus with interferon treatment and continued visiting the hospital for follow-up were also included in the study. A series of 86 eligible patients were invited to participate in the study, of whom 69 (33 men and 36 women) agreed; their average age was 58.5 years (SD = 8.7), and the average duration since the first diagnosis of hepatitis was 113.9 months (SD = 93.1). No patients had a psychiatric diagnosis nor did any regularly take psychotropic agents, except for a short-acting sleep inducer.

Procedure

During a visit to the clinic, the subjects were handed a set of questionnaires and a written consent form. The study participants completed the questionnaires and consent form at home and mailed them to one of the authors; a book of gift certificates worth about $5.00 was then sent to the subjects as gratitude. Besides the Stress Inventory, the subjects also completed a questionnaire that included questions regarding education level, smoking history, alcohol consumption, and history of illness. Biochemical examinations were performed regularly at each visit to the hospital (for most patients, every 2–4 weeks); data for the most recent 4 months were used for the analysis. We classified the subjects into three groups according to the severity of hepatitis as follows: group A, chronic hepatitis with a consistently normal serum alanine aminotransferase level (<40 IU/liter); group B, chronic hepatitis with an elevated alanine aminotransferase level (40 IU/liter or over); and group C, liver cirrhosis; thus, the hepatitis severity of groups A, B, and C was from least to most. Although alanine aminotransferase level is a surrogate measure for severity of hepatitis, a high alanine aminotransferase level was reportedly a strong predictor for hepatocellular carcinoma incidence, and the risk of hepatocellular carcinoma is shown to be low among chronic hepatitis C patients with consistently normal alanine aminotransferase levels.[18,19]

The Stress Inventory

The Stress Inventory is a self-report questionnaire that was developed to assess possible disease-prone personalities and chronic psychosocial stress; its developmental procedures are described elsewhere.[16,17] Briefly, a pool of over 400 items was prepared referring to the Grossarth-Maticek theory of disease-prone personality, including typology,[14,20,21] traits,[22,23] and self-regulation.[24] Relevant constructs and theories proposed by other researchers were also considered, and some were incorporated in the item pool. Starting with these items, a pilot series of interview surveys was performed to obtain valid items by using a variety of subjects, such as medical staff specializing in psychosomatic medicine, psychosomatic patients, and patients with cancer or myocardial infarction. A set of 75 items was revised and selected as appropriate for the Stress Inventory.[16] On the basis of factor analysis, the Stress Inventory was again shortened into 45 items, and 12 scales were constructed; Cronbach's alphas and test-rest reliability coefficients ranged from 0.60 to 0.90 and from 0.66 to 0.82, respectively. The construct validity of these scales was also confirmed through correlation analyses with several conventional questionnaires.[17] The Stress Inventory consists of 12 scales, which are grouped into five based on their developmental process (Appendix 1). Two scales, object dependence of loss and altruism, were developed to represent elements of the construct of the type 1 personality. Low sense of control and unfulfilled need for acceptance have been thought to be common elements of disease-prone personalities, including type 1. Thus, these four scales can be considered type 1-related Stress Inventory scales. The Stress Inventory answers were a 6-point scale, 1 to 6, where 1 and 6, respectively, corresponded to "yes" and "no" or to "almost always" and "rarely." The score of each Stress Inventory item was the average of corresponding item scores and ranges between 1 and 6. We also defined the type 1 score as the average of these scales so that it also ranged between 1 and 6. The type 1 score has an alpha coefficient ranging from 0.69 to 0.73 in different populations (unpublished data).

Analysis

Means of the Stress Inventory scales and type 1 score were calculated according to the severity of chronic hepatitis C (groups A, B, and C), and the corresponding dose responses were tested based on Spearman's rank correlation. Groups B and C were then combined into a severe hepatitis group, leaving group A as the subjects with mild hepatitis. According to the type 1 score, the patients of both groups were categorized into three levels: low, moderate, and high. Cutoff points were determined so that the subjects with mild hepatitis were equally distributed across the three levels. Taking the low score category as a reference, an odds ratio with a 95% confidence interval (CI) of the severe hepatitis, relative to the mild hepatitis for the moderate and high score categories were each estimated by using logistic regression. Adjustment was then made for potential confounding factors, including sex, age, years of education ($\leq$12 versus $\geq$13), smoking history (ever versus never), alcohol consumption (ever versus never), and duration of illness. Computations were performed with SAS software.[25] Reported p values were two-sided, and p values less than 0.05 were regarded as statistically significant.

RESULTS

Table 1 shows demographic, behavioral, and clinical characteristics of the subjects, according to the severity of chronic hepatitis C. The severity was not significantly associated with demographic or behavioral factors, such as age, gender, years of education, smoking history, and drinking history or with duration of illness. It was not surprising that platelet count and serum albumin level were lower and total bilirubin and hepaplastin test levels $<$70% were higher in group C than in groups A or B. The rates of interferon-treated subjects ranged from 42% in group C to 50% in group A. Among those treated with interferon, the rate of success (%), i.e., for acquiring negative viremia, for groups A, B, and C was 9 (64%), 2 (15%), and 0 (0%), respectively.

Table 2 shows the Stress Inventory scale scores, as well as the type 1 score, according to the severity of chronic hepatitis C. The p values for a linear association are also noted in the right column. Each of the four type 1–related Stress Inventory scales—low sense of control, object dependence of loss, unfulfilled need for acceptance, and altruism—was positively and significantly associated with hepatitis severity. The type 1 score was also significantly related to hepatitis severity, with a p value even smaller than those for its elements, the type 1–related Stress Inventory scales. As for the other Stress Inventory scales, no significant association was observed, except that egoism was also positively related.

Because interferon treatment might have caused some alteration in mental status as a side effect[26,27] and because the outcome of interferon therapy, i.e., whether successful

or not, may have affected psychological status, the analysis was repeated for the subgroup that excluded interferon-treated subjects. The results were similar to those for the subjects as a whole: each of the type 1–related Stress Inventory scales and the type 1 score was positively associated with severity. The dose-response relationship for altruism, however, did not clear the significance level (data not shown).

TABLE 1. Demographic, Behavioral, and Clinical Characteristics of Subjects With Chronic Hepatitis C by the Severity of the Illness

	Subjects With Chronic Hepatitis C and Normal Serum Alanine Aminotransferase Level (N = 28)		Subjects With Chronic Hepatitis C and Elevated Serum Alanine Aminotransferase Level (N = 29)		Subjects With Liver Cirrhosis (N = 12)		Analysis		
Characteristic	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**F**	**df**	**p**
Age (years)[a]	57.8	7.6	58.6	10.2	59.8	7.1	0.2	2, 66	0.81
Education (years)	8.6	2.0	9.6	2.9	8.6	1.7	1.4	2, 66	0.26
Duration (months)	104.5	101.1	122.2	95.4	115.4	70.5	0.3	2, 66	0.78
Alanine aminotransferase (IU/liter)	23.4	8.8	76.8	39.9	93.9	98.3	12.8	2, 66	<0.0001
Platelet (count/μl)	17.6	3.8	15.5	4.2	7.7	3.5	27.5	2, 66	<0.0001
Albumin (g/dl)	4.58	0.22	4.49	0.28	4.16	0.43	8.9	2, 66	0.0004
Total bilirubin (mg/dl)	0.76	0.27	0.76	0.28	1.27	0.66	9.3	2, 66	0.0003
	N	**%**	**N**	**%**	**N**	**%**	**χ^2**	**df**	**p**
Female sex	18	64.3	11	37.9	7	58.3	4.2	1	0.12
Ever smoker	9	32.1	10	34.5	3	25.0	0.4	1	0.84
Ever drinker	8	28.6	8	27.6	4	33.3	0.1	1	0.93
Hepaplastin level <70%	0	0.0	1	3.5	6	50.0	0.3	1	<0.0001[a]
Treated with interferon alpha	14	50.0	13	44.8	5	41.7			0.87

[a]Fisher's exact test.

TABLE 2. Type-1–Related Stress Inventory Scale Scores and Other Stress Inventory Scores Related to Severity of Hepatitis C

	Subjects With Chronic Hepatitis C and Normal Serum Alanine Aminotransferase Level (N = 28)		Subjects With Chronic Hepatitis C and Elevated Serum Alanine Aminotransferase Level (N = 29)		Subjects With Liver Cirrhosis (N = 12)		
Stress Inventory Item	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**p[a]**
Type-1–related scales							
Low sense of control	3.29	1.62	3.94	1.34	4.60	1.17	0.009
Object dependence of loss	2.45	1.20	3.09	1.21	3.77	1.36	0.003
Unfulfilled need for acceptance	2.91	1.24	3.53	1.40	4.27	1.30	0.004
Altruism	3.07	1.25	3.50	1.14	4.17	0.88	0.006
Other scales							
Object dependence of happiness	2.29	1.45	2.64	1.51	3.13	1.73	0.11
Object dependence of anger	2.83	1.36	2.95	1.43	3.60	1.36	0.23
Annoying barrier	3.59	1.87	3.28	1.65	4.21	1.67	0.66
Object dependence of ambivalence	2.04	0.91	1.95	1.00	2.46	1.21	0.62
Disclosure of negative experiences	3.49	1.73	3.76	1.68	3.52	1.29	0.67
Egoism	3.25	1.07	3.77	1.15	3.92	1.18	<0.03
Rationalizing conflict or frustration	3.99	1.23	4.03	1.20	3.80	1.08	0.74
Lacking emotional experiences	2.22	0.92	2.58	1.12	2.13	1.03	0.85
Type-1 score	2.93	0.95	3.52	0.94	4.20	0.62	<0.0001

[a]Based on Spearman's rank correlation.

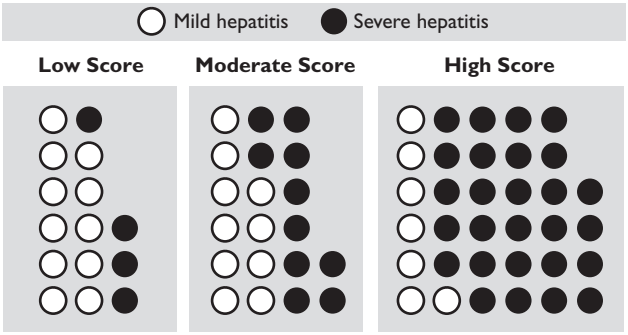
Figure 1 shows the distribution of severe and mild hepatitis according to the type 1 score, as well as the corresponding odds ratios. The patients with chronic hepatitis C with the highest level of type 1 score were at more than a 10-fold higher risk of having severe hepatitis than were those with the lowest score level. When the potential cofounders, including age, sex, years of education, smoking status, alcohol consumption, and duration were adjusted, the odds ratios (with 95% CI) for the moderate and highest type 1 scores were 2.5 (95% CI = 0.6–11.4) and 15.0 (95% CI = 3.4–65.0), respectively, compared with the lowest score (p for trend <0.0001).

DISCUSSION

The present study showed that the type 1 personality, as well as its elemental traits—low sense of control, object dependence of loss, unfulfilled need for acceptance, and altruism—were each significantly and positively associated with the severity of chronic hepatitis C. Such a personality or chronic psychosocial stress, as indicated by these constructs, might play the role of host factor in the progression of chronic hepatitis C. To our knowledge, no previous study has found the relationship between psychosocial factors and the severity of chronic hepatitis C. Kunkel et al.[28] showed that transaminase levels were positively correlated with the degree of depression, measured by the short form of the Beck Depression Inventory, in patients with chronic hepatitis B.

While acute stress may be associated with transient immune activation, chronic stress seems more consistently associated with immune downregulation or depression.[29,30] Several studies have agreed that a lower number or activity of natural killer cells, which play a crucial role in the clearance of virus-infected cells,[31] was associated with chronic stress, such as chronic professional stress,[32] bereavement,[33] loneliness,[34] and distress after a hurricane.[35] Bonavita et al.[36] examined the activity of natural killer cells in patients with chronic hepatitis C before and after an interferon-alpha treatment. Before the treatment, natural killer cell activity was below the normal range for all of their subjects. Patients in whom natural killer cell activity normalized had a significantly lower frequency of relapse, which was defined by alanine aminotransferase levels returning to pretherapy values within 3 months, compared to those in whom natural killer cell activity continued below the normal range until the end of treatment. In addition, in a prospective study, Nakajima et al.[37] showed that patients with liver cirrhosis with decreased natural killer cell activity were at a higher risk of developing hepatocellular carcinoma than those with normal natural killer cell activity. Since the type 1 personality and related elements represent chronic stress or personalities prone to chronic distress, the association with hepatitis severity might partly be explained by such immunodepression as lowered natural killer cell activity. The present study, however, did not examine immunological parameters.

FIGURE 1. The Distribution of Mild and Severe Hepatitis by the Type 1 Score and Corresponding Odds Ratios[a]



[a]Low score: odds ratio = 1 (reference); moderate score: odds ratio = 2.8 (confidence interval = 0.7–11.6); high score: odds ratio = 10.6 (confidence interval = 2.6–43.6).

The four type 1–related personality traits were each associated with the severity of chronic hepatitis C. There are several reports that link psychosocial variables thought to be closely related to these traits at the onset and progression of chronic viral infection. For example, a low sense of control is thought to lead to a chronic negative mood, and the negative mood status was shown to be related to more frequent recurrences of genital herpes.[4] Unfulfilled need for acceptance shares a common concept with repression of emotion, the relevant constructs of which were reported to be associated with the progression of HIV infection.[8,9] This trait may also relate to the concept of social support, more specifically a lack of emotional support, which is suggested to be potentially important in the progression of HIV infection.[11] It should also be noted that the type 1 score, which was defined as the average of the type 1–related Stress Inventory scales, seemed even more strongly associated with the severity of chronic hepatitis C than any single elemental trait. This suggests that a combination rather than any one of the traits may be more relevant in accounting for the contribution of psychosocial factors to immunological regulation in chronic viral infection.

The potential effect of interferon treatment must be considered when interpreting the present results. Interferon is known to cause psychiatric side effects, including severe depression.[26,27] The present study did not include patients

who had undergone interferon treatment within the past 6 months. However, this may not completely preclude the possibility that the interferon treatment had caused a sustained alteration in the subjects' mental status. Another concern regarding interferon therapy relates to the fact that the success rate of the treatment differed greatly between group A and groups B and C. Interferon treatment success would no doubt uplift the patient's mood,[38] while a failure could cause serious disappointment, possibly leading to depression. However, even when the subjects were limited to those without interferon treatment, the association with the type 1 and related Stress Inventory scales were similar to the results from the subjects as a whole.

Being of cross-sectional design, the present study cannot conclusively show that the type 1 personality was *causally* associated with the severity of chronic hepatitis C. When a patient knows that his hepatitis has continued in an unfavorable state, e.g., alanine aminotransferase levels were continuously elevated, such information per se would cause distress. In a previous investigation,[17] the type 1-related Stress Inventory scales were positively correlated with both depression and anxiety. However, other scales that were also positively correlated with depression and anger, such as object dependence of anger, annoying barriers, and object dependence of ambivalence, were not as clearly associated with hepatitis severity as the type 1-related scales. Also of concern is that a more severe hepatitis status might have caused a decrease in physical function and, as result, a more negative affective state. However, even in group B, in which liver function virtually stayed within a compensated stage (Table 1), the scores of the type 1-related scales and the type 1 score tended to be higher than in group A. In addition, disease severity in chronic hepatitis C seems not always to be associated with a negative affective state.[39–41] A negative affective state, which might have been caused by the patients' awareness of their disease status or lowered physical function because of advanced hepatitis, would not fully explain the observed strong association between hepatitis severity and the type 1 personality. Nevertheless, the present findings should be confirmed in future studies that measure negative affective states such as depression and anxiety as well and preferably of a prospective design.

Funded in part by a grant from the MOA Health Science Foundation.

The authors thank Kei Nakachi and Kazue Imai of the Radiation Effects Research Foundation for their comments on interpretation of the results and Akiko Noguchi, Kazuko Yasukawa, and Vernon Sullivan for technical assistance.

APPENDIX 1. A Brief Description of the Stress Inventory Scales

Group 1
1. Low sense of control: decreased sense of control over stressful situations, leading to hardship, despair, or anger.

Group 2
2. Object dependence of loss: having an important person in one's life who causes persistent hopelessness and depression.
3. Object dependence of happiness: having a highly valued person in one's life on whom one's happiness is greatly dependent.
4. Object dependence of anger: having a persecuting person who causes chronic irritation and anger.
5. Annoying barrier: having a persecuting situation that causes chronic irritation and anger.
6. Object dependence of ambivalence: repeatedly experiencing highly ambivalent interpersonal relationships.

Group 3
7. Disclosure of negative experiences: a tendency to disclose one's experiences regarding negative feelings toward others.
8. Unfulfilled needs for acceptance: chronically having an unfulfilled need for acceptance by others.

Group 4
9. Altruism: an altruistic tendency, accompanied by stress, in interpersonal and social relationships.
10. Egoism: a self-defensive, self-interest-oriented attitude in interpersonal and social relationships.
11. Rationalizing conflicts and frustrations: an extreme tendency to rationalize one's interpersonal situations, accompanied by conflicts or frustrations.

Group 5
12. Lacking emotional experiences: lack of experience with strong emotions, such as grief, rage, or delight.

References

1. Marcellin P: Hepatitis C: the clinical spectrum of the disease. J Hepatol 1999; 31(suppl 1):9–16
2. Nguyen HA, Ho SB: Natural history of chronic hepatitis C: identifying a window of opportunity for intervention. J Lab Clin Med 2001; 137:146–154
3. Lin OS, Keeffe EB: Current treatment strategies for chronic hepatitis B and C. Annu Rev Med 2001; 52:29–49
4. Kemeny ME, Cohen F, Zegans LS, Conant MA: Psychological and immunological predictors of genital herpes recurrence. Psychosom Med 1989; 51:195–208

5. Dalkvist J, Wahlin TB, Bartsch E, Forsbeck M: Herpes simplex and mood: a prospective study. Psychosom Med 1995; 57:127–137
6. Schmader K, Studenski S, MacMillan J, Grufferman S, Cohen HJ: Are stressful life events risk factors for herpes zoster? J Am Geriatr Soc 1990; 38:1188–1194
7. Irwin M, Costlow C, Williams H, Artin KH, Chan CY, Stinson DL, Levin MJ, Hayward AR, Oxman MN: Cellular immunity to varicella-zoster virus in patients with major depression. J Infect Dis 1998; 178(suppl 1):S104–S108; correction, 1999; 179:753
8. Cole SW, Kemeny ME, Taylor SE, Visscher BR: Elevated physical health risk among gay men who conceal their homosexual identity. Health Psychol 1996; 15:243–251
9. Cole SW, Kemeny ME, Taylor SE, Visscher BR, Fahey JL: Accelerated course of human immunodeficiency virus infection in gay men who conceal their homosexual identity. Psychosom Med 1996; 58:219–231
10. Mayne TJ, Vittinghoff E, Chesney MA, Barrett DC, Coates TJ: Depressive affect and survival among gay and bisexual men infected with HIV. Arch Intern Med 1996; 156:2233–2238
11. Leserman J, Jackson ED, Petitto JM, Golden RN, Silva SG, Perkins DO, Cai J, Folds JD, Evans DL: Progression to AIDS: the effects of stress, depressive symptoms, and social support. Psychosom Med 1999; 61:397–406
12. Lewis C, O'Sullivan C, Barraclough J (ed): The Psychoimmunology of Cancer: Mind and Body in the Fight for Survival? New York, Oxford University Press, 1994
13. Garssen B, Goodkin K: On the role of immunological factors as mediators between psychosocial factors and cancer progression. Psychiatry Res 1999; 85:51–61
14. Grossarth-Maticek R, Eysenck HJ, Vetter H: Personality type, smoking habit and their interaction as predictors of cancer and coronary heart disease. Pers Individ Dif 1988; 9:479–495
15. Grossarth-Maticek R, Eysenck HJ, Boyle GJ, Heep J, Costa SD, Diel IJ: Interaction of psychosocial and physical risk factors in the causation of mammary cancer, and its prevention through psychological methods of treatment. J Clin Psychol 2000; 56:33–50; correction, 2000; 56:829
16. Nagano J, Sudo N: [Development of a self-administered questionnaire to assess disease-prone personalities: item construction and content validity.] Kenko Kagaku (Journal of Health Science) 2001; 23:41–52 (Japanese)
17. Nagano J, Sudo N, Kaihara C: [Validity and reliability of the Stress Inventory: self-administered questionnaire to assess disease-prone personalities.] Kenko Shien (Jpn J Health Promotion) 2001; 3:107–119 (Japanese)
18. Tanaka K, Sakai H, Hashizume M, Hirohata T: A long-term follow-up study on risk factors for hepatocellular carcinoma among Japanese patients with liver cirrhosis. Jpn J Cancer Res 1998; 89:1241–1250
19. Hayashi J, Furusyo N, Ariyama I, Sawayama Y, Etoh Y, Kashiwagi S: A relationship between the evolution of hepatitis C virus variants, liver damage, and hepatocellular carcinoma in patients with hepatitis C viremia. J Infect Dis 2000; 181:1523–1527
20. Grossarth-Maticek R, Eysenck HJ: Personality, stress and disease: description and validation of a new inventory. Psychol Rep 1990; 66:355–373
21. Nagano J, Sudo N, Kubo C, Kono S: Lung cancer, myocardial infarction, and the Grossarth-Maticek personality types: a case-control study in Fukuoka, Japan. J Epidemiol 2001; 11:281–287; correction, 2002; 12:188
22. Grossarth-Maticek R: Psychosocial predictors of cancer and internal diseases: an overview. Psychother Psychosom 1980, 33:122–128
23. Grossarth-Maticek R, Bastiaans J, Kanazir DT: Psychosocial factors as strong predictors of mortality from cancer, ischaemic heart disease and stroke: the Yugoslav prospective study. J Psychosom Res 1985; 29:167–176
24. Grossarth-Maticek R, Eysenck HJ: Self-regulation and mortality from cancer, coronary heart disease, and other cause: a prospective study. Pers Individ Dif 1995; 19:781–795
25. SAS/STAT User's Guide, version 6.03. Cary, NC, SAS Institute, 1988
26. Dieperink E, Willenbring M, Ho SB: Neuropsychiatric symptoms associated with hepatitis C and INF alpha: a review. Am J Psychiatry 2000; 157:867–876
27. Yovtcheva SP, Rifai MA, Moles JK, Van der Linden BJ: Psychiatric comorbidity among hepatitis C-positive patients. Psychosomatics 2001; 42:411–415
28. Kunkel EJ, Kim JS, Hann HW, Oyesanmi O, Menefee LA, Field HL, Lartey PL, Myers RE: Depression in Korean immigrants with hepatitis B and related liver diseases. Psychosomatics 2000; 41:472–480
29. Olff M: Stress, depression and immunity: the role of defense and coping styles. Psychiatry Res 1999; 85:7–15
30. Biondi M: Effects of stress on immune functions: an overview, in Psychoneuroimmunology, 3rd ed, vol 2. Edited by Ader R, Felten D, Cohen N. San Diego, Calif, Academic Press, 2001, pp 189–226
31. Biron CA, Nguyen KB, Pien GC, Cousens LP, Salazar-Mather TP: Natural killer cells in antiviral defense: function and regulation by innate cytokines. Annu Rev Immunol 1999; 17:189–220
32. De Gucht V, Fischler B, Demanet C: Immune dysfunction associated with chronic professional stress in nurses. Psychiatry Res 1999; 85:105–111
33. Irwin M, Daniels M, Risch SC, Bloom E, Weiner H: Plasma cortisol and natural killer cell activity during bereavement. Biol Psychiatry 1988; 24:173–178
34. Kiecolt-Glaser JK, Ricker D, George J, Messick G, Speicher CE, Garner W, Glaser R: Urinary cortisol levels, cellular immunocompetency, and loneliness in psychiatric inpatients. Psychosom Med 1984; 46:15–23
35. Ironson G, Wynings C, Schneiderman N, Baum A, Rodriguez M, Greenwood D, Benight C, Antoni M, LaPerriere A, Huang HS, Klimas N, Fletcher MA: Posttraumatic stress symptoms, intrusive thoughts, loss, and immune function after Hurricane Andrew. Psychosom Med 1997; 59:128–141
36. Bonavita MS, Franco A, Paroli M, Santilio I, Benvenuto R, De Petrillo G, Levrero M, Perrone A, Balsano C, Barnaba V: Normalization of depressed natural killer activity after INF-alpha therapy is associated with a low frequency of relapse in patients with chronic hepatitis C. Int J Tissue React 1993; 15:11–16
37. Nakajima T, Mizushima N, Kanai K: Relationship between natural killer activity and development of hepatocellular carcinoma in patients with cirrhosis of the liver. Jpn J Clin Oncol 1987; 17:327–332
38. Bonkovsky HL, Woolley JM (Consensus INF Study Group): Reduction of health-related quality of life in chronic hepatitis C and improvement with INF therapy. Hepatology 1999; 29:264–270
39. Foster GR, Goldin RD, Thomas HC: Chronic hepatitis C virus infection causes a significant reduction in quality of life in the absence of cirrhosis. Hepatology 1998; 27:209–212
40. Dwight MM, Kowdley KV, Russo JE, Ciechanowski PS, Larson AM, Katon WJ: Depression, fatigue, and functional disability in patients with chronic hepatitis C. J Psychosom Res 2000; 49:311–317
41. Kraus MR, Schafer A, Csef H, Scheurlen M, Faller H: Emotional state, coping styles, and somatic variables in patients with chronic hepatitis C. Psychosomatics 2000; 41:377–384