CORRESPONDENCE

Brain-Derived Neurotrophic Factor Predicts Physical Health in Untreated Patients with Hepatitis C

To the Editor:

Brain-derived neurotrophic factor (BDNF), as the most abundant growth factor in the brain, has several functions in neural development and regeneration (1). This factor may be involved in mood disorders, cognitive problems, and chronic fatigue syndrome (1–3). Hepatitis C virus (HCV) is thought to cause neuropsychiatric symptoms, such as mood disturbances, fatigue, and impaired physical and mental aspects of quality of life independent of the disease activity, or cirrhosis (4,5). In one study, patients with HCV had lower physical health scores but similar mental health scores compared with patients with hepatitis B virus (HBV) (5). Many authors have argued that these symptoms might be related to using interferon, drug abuse, or disease chronicity (4,6), while others believe that these symptoms may reflect some kind of brain involvement in patients with HCV (7).

Considering evidences of brain involvement in patients with HCV along with some similarities between neuropsychiatric symptoms of HCV and neuropsychiatric symptoms associated by impaired BDNF production, we hypothesized that some of these symptoms might be associated with reduced BDNF levels. To test this hypothesis, we selected a homogenous group of noncirrhotic male patients with HCV ($n = 40$) who were not treated with interferon, had not used illicit drugs or alcohol for at least 6 months, did not have concomitant hepatitis B or human immunodeficiency virus, and had not suffered from severe psychiatric disorders (group 1). We also included a group of male patients with HBV ($n = 31$) with the same inclusion criteria as a comparison group (group 2) to control for both disease chronicity and hepatic involvement. We then administered three questionnaires, Short Form-36 (SF-36), Iowa Fatigue Scale, and Hospital Anxiety and Depression Scale to these patients. Blood was drawn in the morning for measurement of BDNF (Promega Enzyme-Linked Immunosorbent Assay kits, Madison, Wisconsin), as well as liver enzymes, hemoglobin, and thyroid function tests. In addition, 25 patients with HCV had liver biopsy within 1 month of blood sampling. Patients gave informed consent and the Ethics Committee of Digestive Disease Research Center of Shariati Hospital, Tehran, Irân, approved the study.

Depression, anxiety, and mental component summary of SF-36 did not differ significantly between the two groups. However, physical component summary (PCS) of SF-36 was significantly different between group 2 and group 1 (50.56 ± 6.6 and 43.97 ± 10.0, respectively, $p < .01$). BDNF levels were significantly different between patients with HBV and HCV (159.4 ± 43.8 vs. 140.5 ± 35.4 pg/mL, respectively, $p < .05$). Scores of PCS were significantly correlated with BDNF levels in patients with HCV but not HBV ($r = .383$, $p < .05$ for HCV, and $r = -.172$, $p = .47$ for HBV). Scores of PCS and fatigue scale were not correlated with hemoglobin, liver enzymes, and thyroid function tests in the HBV group. In the HCV group, hemoglobin was significantly correlated with PCS. Ishak score did not correlate with patient scores or BDNF levels. To minimize the confounding effect of anxiety and depression, we divided our patients into two groups based on the Hospital Anxiety and Depression Scale scores: without anxiety and depression (score of less than 10 on each subscale) and with anxiety or depression. In patients with HCV who were neither anxious nor depressed, the PCS scores correlated significantly with BDNF levels ($r = .663$, $p < .01$). Because BDNF and cigarette smoking are positively correlated with each other, we performed a multiple regression analysis with BDNF and pack year of cigarette smoking, together with hemoglobin, once in all patients with HBV or HCV (separately) and a second time in separate groups of patients based on hepatitis status and anxiety and depression status. The best model for patients with HCV consisted of BDNF (standardized beta = .403) and smoking (standardized beta = −.490) with an adjusted R^2 of .477. Multiple regression model in nonanxious, nondepressed patients with HCV showed BDNF (standardized beta = .712) and pack year of cigarette smoking (standardized beta = −.475) are strong predictors of PCS (adjusted $R^2 = .632$). These patients also showed a significant negative correlation between fatigue subscale energy and BDNF levels ($r = -.421$, $p < .05$). Cigarette smoking was the only predictor of PCS in anxious or depressed patients with HCV (standardized beta = −.758, adjusted $R^2 = .503$). None of these variables predicted PCS in patients with HBV.

To the best of our knowledge, this was the first study that showed the possibility of BDNF involvement in the impaired physical function and fatigue of untreated patients with HCV. This finding supports the brain involvement in patients with HCV (7). Some points, however, should be taken into account. Messenger RNA of several neural growth factors are produced in stellate cells in the liver, and because these cells are hyperactive in the inflammatory status, increased BDNF level may be a marker of increased inflammation and fibrosis and may be totally irrelevant to the brain involvement in these patients (8). If this is true, then increased fibrosis should be concomitant with increased BDNF levels, and increased BDNF levels correspond to better PCS. Actually, this is not the case, because some studies showed that with increasing level of fibrosis, patients became more physically disabled (9), and in some studies (like ours), no association was found between fatigue and fibrosis in patients with HCV (10,11). Lower BDNF and PCS scores in HCV compared with HBV and relation of BDNF levels to PCS scores in HCV but not HBV suggest that the origin of these processes may not be in the liver. A correlation has been shown between fatigue and PCS in patients with chronic fatigue syndrome (12). Therefore, a hypothesis that should be further tested is that whether BDNF has a role in chronic fatigue syndrome in these patients.

This is the first study (to our knowledge) that provided evidence for association of BDNF with impairment of physical aspects of quality of life in patients with HCV. Furthermore, we were able to document that this association is independent from alcohol and drug abuse status, cigarette smoking, mood problems, cirrhosis and hepatic involvement, and treatment with interferon. To investigate this role in more detail, further studies with objective instruments, as well as studies with combined neuroimaging and measurement of BDNF, are warranted.

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