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Depression and neuroticism in patients with chronic hepatitis C: Correlation with peripheral blood mononuclear cells activation

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ABSTRACT

Background: Hepatitis C virus (HCV) infection is commonly associated with cognitive dysfunction and depression, which could be related to direct brain infection. Viral sequences and proteins were found in brain macrophage/microglia cells and these cells were reported to be activated. Since blood leukocytes cross blood–brain barrier, activation state of peripheral blood mononuclear cells (PBMC) could reflect the state of brain immune cells.
Objective: The aim of the study was to determine whether depression and neuroticism in chronic HCV infection correlates with the expression of key cytokines and chemokines in PBMC.
Design: We studied 24 HCV-positive patients undergoing treatment with interferon and ribavirin. Patients were tested for depression using Beck Depression Inventory (BDI) and Montgomery Åsberg Depression Rating Scale (MADRS), while neuroticism was assessed by the Revised Eysenck Personality Inventory (N/EPO-R). Transcripts representing 28 various cytokines and chemokines were measured by real-time quantitative PCR in PBMC.
Results: Prior to therapy BDI and MADRS positively correlated with viral load while neuroticism correlated with IL-3, IL-8 and M-CSF transcription levels. Six months after therapy there was positive correlation between depression and/or neuroticism scores and the levels of proinflammatory cytokines TNF-α and IL-12 transcripts, as well as IL-8, IL-10, IL-16, MCP-1, MCP-2, MIP-1-alpha, MIP-1-beta, and TGF-beta, and IFN-β transcripts.
Conclusion: Activation of PBMC, as measured by the level of cytokine and chemokine transcripts, correlates with depression and neuroticism scores. These findings suggest a pivotal role of immune cells activation in depression and possibly neurocognitive dysfunction among chronic hepatitis C patients.

1. Background

Patients with chronic hepatitis C virus (HCV) infection were reported to suffer from depression and cognitive dysfunction [1–3]. The reasons behind this phenomenon were largely unclear, but it was suspected that they could be related to the psychological burden of chronic illness and/or liver dysfunction. However, Forton and colleagues demonstrated elevations of choline/creatine ratios in basal ganglia and white matter in patients with hepatitis C by proton magnetic-resonance spectroscopy (^{1}H MRS) thus providing evidence for the likely biological basis of HCV-related brain effects. Such changes were not present either in healthy volunteers or patients with hepatitis of other etiology [2,4] and were clearly different from those seen in hepatic encephalopathy, where the choline ratios are depressed [5]. Notably, they are similar to findings reported in patients with HIV infection, where virus replicates in the central nervous system [6,7]. The original findings reported by Forton were since confirmed by other groups [8,9].

The results of the above studies raised the possibility that HCV could be neurotropic. Indeed, negative-strand HCV RNA, which is viral replicative intermediate, was subsequently detected in autopsy brain tissue [10] and two other studies demonstrated the

Abbreviations: HCV, hepatitis C virus; PBMC, peripheral blood mononuclear cells; BDI, Beck Depression Inventory; MADRS, Montgomery Åsberg Depression Rating Scale; N/EPO-R, Revised Eysenck Personality Inventory.

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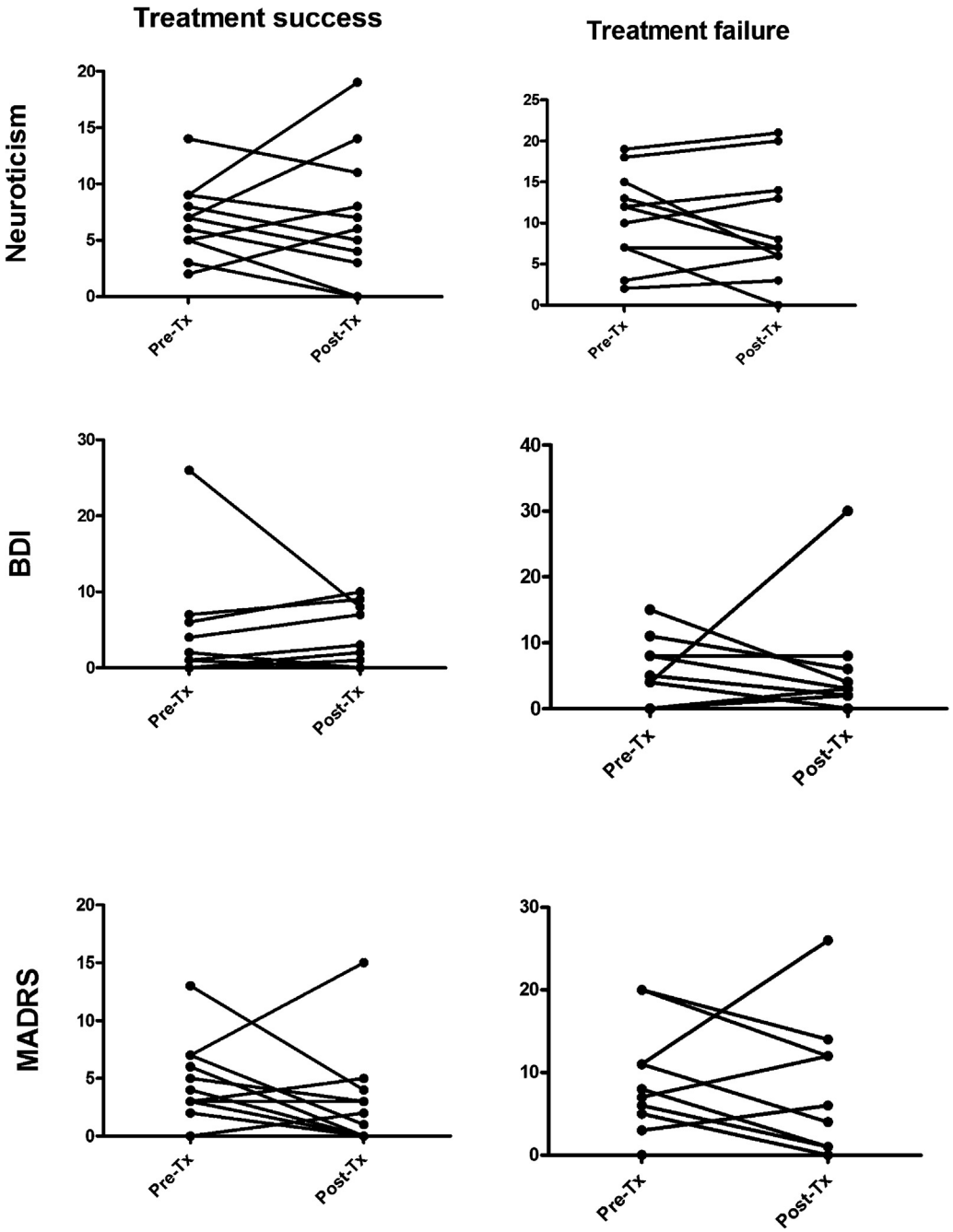

Fig. 1. Neuroticism and Depression in patients with chronic HCV infection treated with Interferon and Ribavirin. Neuroticism was assessed by the Revised Eysenck Personality test, while depression was measured by Back Depression Index (BDI) and Montgomery Åsberg Depression Rating Scale (MADRS). Twelve patients were sustained virological responders (treatment success) and 12 remained HCV RNA positive (treatment failure). Psychological evaluation was done right before (pre-Tx) and 6 months after the end of treatment (post-Tx). Data were compared using the nonparametric Wilcoxon matched pairs test (NS).

presence of HCV proteins in brain tissue by Western blotting and/or immunostaining [11,12]. Furthermore, brain-derived HCV variants were found to be distinct from those circulating in blood, thus suggesting the presence of separate CNS compartment [10,13].

The cells harboring HCV in the brain were identified by two independent groups as astrocytes and macrophages/microglia cells [11,12]. It has been established that all basic groups of leukocytes: T-cells, B-cells, macrophage/monocytes and NK-cells, have the ability to enter the brain under certain conditions [14] and some monocyte family members are constantly being replaced as part of normal physiology [15,16]. Thus it could be speculated that the activation state of lymphoid cells circulating in the blood could reflect the activation of those in the brain.

2. Objectives

The aim of the study was to determine whether depression and neuroticism in chronic HCV infection correlates with the expression of key cytokines and chemokines in PBMC.

3. Study design

3.1. Patients

The current study was nested within a larger study analyzing the effect of interferon treatment on neuroticism and depression in patients with chronic hepatitis C (study still in progress).