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Depressive symptoms and cognitive dysfunction in patients with hepatitis C treated with interferon-α and ribavirine

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Summary

Aim. The purpose of the study was an assessment of the prevalence of depressive symptoms and characteristic of cognitive functions in patients with hepatitis C before and after three month treatment with interferon-α plus ribavirine.

Subject and methods. One hundred hepatitis C patients without decompensated liver function and without organic or psychotic disorder were assessed using the Hamilton Depression Rating Scale, the Stroop Test and the Trail Making Test.

Results. Significant depressive symptoms were present in 18% patients at enrolment. Three-month therapy with IFN+RBV brought about depressive symptoms in additional 25% patients and did not influence their cognitive functions. Patients who had depression at enrolment exhibited significant worse verbal working memory than patients with interferon-α induced depression at the second assessment. Patients without depressive symptomatology both before and after IFN+RBV therapy significantly improved on tests of psychomotor speed and verbal working memory after three-month IFN+RBV therapy.

Conclusion. Clinical and neuropsychological differences may suggest distinct pathogenesis of spontaneous and interferon-induced depression.

hepatitis C / interferon / depression / cognitive functions

INTRODUCTION

Hepatitis C is currently a significant medical problem worldwide. The WHO estimates that as much as 3% of the general population may be carriers of the hepatitis C virus (HCV). Chronic C hepatitis may cause liver neoplasmatic diseases or liver degeneration in a substantial part of patients [1]. Even without fatal somatic consequences, patients with chronic hepatitis C may suffer from encephalopathy [2, 3, 4, 5, 6].

Treatment of choice for chronic hepatitis C is 6 or 12 month administration of pegylated interferon-α (given subcutaneously once a week) plus ribavirine (given twice a day orally) [1, 7]. Interferon (IFN)-α is a cytokine that is produced in response to viral infection. It may intrude to the brain in the periaqueductal area of the hypothalamus and may influence activity of different types of neurons [8, 9]. Interferon-α may induce changes in function of other cytokines and

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hypothalamic-pituitary axis activation resulting in hypercortisolemia [8, 10]. In consequence, it directly and indirectly modulates serotoninergic, dopaminergic, glutaminergic and opioid neurons [11, 12]. IFN-α, unlike IFN β and γ, increases time of inhibition on the forced swimming test in animals and this indicates a depressiogenic action of this compound [13]. The PET study revealed IFN-α induced reduction of glucose metabolism in prefrontal and right parietal cortex as well as glucose hypermetabolism in the striatum and posterior part of the right thalamus. The decrease in prefrontal glucose metabolism significantly correlated with the Beck Depression Inventory score [14]. Ribavirine (RBV) is a nucleoside analogue which has immunomodulative properties and exerts its action onto many viruses. Neuropsychiatric side effects of RBV were not observed [1, 7, 15].

On the other hand, depressive and anxiety disorders or fatigue are frequently encountered neuropsychiatric side effects of IFN-α [16, 17, 18]. Even 35% hepatitis C patients treated with IFN+RBV may suffer from a depressive disorder and this is the most common reason for premature termination of anti-HCV therapy [7]. Therefore, SSRI treatment in patients with depressive symptoms is recommended both before and during IFN+RBV therapy [19, 20, 21].

Neurocognitive changes in patients with hepatitis C receiving IFN+RBV were not comprehensively studied. Significantly increased reaction times and greater number of false reactions indicating attention dysfunction was described in the group of 70 patients [22]. Functional magnetic resonance imaging during a task of visuospatial attention revealed evidence of greater mental effort in patients with hepatitis C treated with IFN+RBV than in healthy control subjects [23]. Performance on the Stroop Test and the Trail Making Test of 20 patients with hepatitis C treated with pegylated interferon plus ribavirin did not change during the 6 month therapy [24].

AIM OF THE STUDY

The purpose of the study was an assessment of the prevalence of depressive symptoms and cognitive dysfunctions in patients with hepatitis C before and after three month treatment with pegylated interferon plus ribavirine.

SUBJECT AND METHODS

One hundred patients with morphologically, serologically, virogically and biochemically confirmed hepatitis C were enrolled. The excluding criteria were substance abuse, a psychotic disorder and an organic mental disorder. Psychometric assessment and cognitive performance were done twice: before IFN+RBV initiation and after the three month treatment. Depressive symptomatology was noted with the Hamilton Depression Rating Scale, 17-item version [25, 26]. Cut-off for diagnosing clinically significant depression was 12 points since the threshold differentiates reasonably well outpatients with depression from the general population [27]. The patients who had 12 or more points at enrolment were offered treatment with a SSRI (citalopram, escitalopram) or tianeptine which are regarded as both safe and efficacious in treatment of depression in patients with liver illnesses [16, 21, 28, 29].

Brief neuropsychological assessment with the Stroop Test A&B and the Trail Making Test A&B to evaluate psychomotor speed, attention and working memory was also done twice: before and after the three month treatment with IFN+RBV [30, 31, 32]. The study was approved by the local Bioethic Committee.

RESULTS

One hundred Caucasian patients with serologically confirmed hepatitis C but without widely progressed or decompensated liver disease were recruited. The sample consisted of 54 males, 46 females, aged 39.5 ± 13 years (min. 18, max. 65). Mean duration of education was 13 ± 2 years.

Three subgroups were compared:

Patients with significant depressive symptoms present before treatment with IFN + RBV (n=18; 4 males, 14 females) who were treated with an antidepressant during the study

Patients without significant depressive symptoms at the beginning of the study, but with significant depressive symptoms after three month

treatment with IFN + RBV (n=25; 16 males, 9 females)

Patients without depressive symptoms both at the beginning and after three month treatment with IFN + RBV (n=57; 34 males, 23 females).

Significant depressive symptoms were present in 18% patients with hepatitis C before therapy with IFN+RBV and additional 25% became depressive during three month therapy with IFN+RBV. In aggregate 43 out of 100 hepatitis C patients (20 males and 23 females) indications for antidepressant therapy existed either before or after three month therapy with IFN+RBV.

Intensity of depressive symptoms was considerably greater at the beginning of the study in group 1 than in other groups and did not change significantly after three month therapy with IFN+RBV. Severity of depression was significantly greater after three month IFN+RBV therapy in the group 2 than in the group 1. Depressive symptomatology became remarkably more pronounced in both group 2 and 3 after three month therapy with IFN+RBV (Tab.1).

Table 1. Hamilton Depression Rating Scale scores of CHC patients. Median value (25–75%)

	group 1 (n=18)	group 2 (n=25)	group 3 (n=57)
before IFN-α+RBV	16 (13-21)**#	3 (2-5)	2 (1-4)
after 3 mo IFN-α+RBV	13 (9-21)*#	18 (14-23)& †	4 (2-5) †

group 1 - patients with depressive symptomatology prior to treatment with IFN-α+RBV

group 2 - patients with depressive symptomatology after three-month treatment with IFN-α+RBV

group 3 - patients with no depressive symptoms

† - p<0.001: Wilcoxon test, difference between before vs. after treatment;

Mann-Whitney test:

* - difference between group 1 and 2: p<0.05

** - difference between group 1 and 2: p<0.001

- difference between group 1 and 3: p<0.001

& - difference between group 2 and 3: p<0.001

The compared groups did not differ significantly as for the years of education. In the group of patients with notable depressive symptomatology at enrolment the percentage of females (78%) was significantly greater than in the group without depressive symptoms (40%) and the group with interferon-α induced depression (36%) (χ2 test, p<0.01). Patients from the group with depressive symptomatology at enrolment was significantly older than patients of group 2 (U test, p<0.01).

No significant differences between groups in performance on the Stroop Test A&B (time and number of errors), TMT A&B before IFN+RBV and also on Stroop Test A and TMT A&B after three-month treatment with IFN+RBV were observed. Patients with depressive symptoms at enrolment exhibited significantly worse verbal working memory after three-month IFN+RBV therapy than patients with interferon-α depression (U test, p<0.05). Patients without depressive symptomatology both before and after IFN+RBV therapy exhibited significant improvement of psychomotor speed (Wilcoxon test, p<0.05) and verbal working memory after three-month IFN+RBV therapy (Wilcoxon test, p<0.01). Interferon-α induced depression but did not influence cognitive functions in patients of group 2 (Tab. 2, on the next page).

DISCUSSION

Depressive symptoms are encountered in 10-28% patients with hepatitis C [33, 34, 35]. The percentage of patients with hepatitis C in our study who had depression before IFN+RBV treatment is similar to the percentage of primary care patients with depressive disorders [36].

In the Italian study major depression was diagnosed in 11 (40.7%) of 27 hepatitis C patients after three month treatment with IFN-α and ribavirine [37]. In the Greek study, 19% of 36 patients had major depressive (MD) disorder before IFN+RBV initiation and additional 25% patients developed MD during therapy. Antidepressant treatment resulted in a significant decrease of depressive symptomatology assessed with the Hamilton Depression Rating Scale [38]. Depressive symptoms assessed with the self-rating scale were moderate to severe in 39% patients throughout 24 weeks of treatment with IFN+RBV [39]. Results of our study correspond well with results of other surveys on the prevalence of depressive disorders before and after treatment with IFN+RBV in patients with hepatitis C.

Table 2. Performance of CHC patients treated with interferon-α plus ribavirin on the Trail Making Test and the Stroop Test B. Median value (25-75%)

		group 1 (n=18)	**group 2** (n=25)	**group 3** (n=57)
TMT A (sec.)	before IFN-α+RBV	32 (25-37)	25 (20-35)	28 (22-35)
	after 3 mo IFN-α+RBV	33 (24-42)	27 (19-32)	25 (20-34) †
TMT B (sec.)	before IFN-α+RBV	73 (60-90)	65 (52-81)	70 (55-84)
	after 3 mo IFN-α+RBV	66 (56-110)	60 (45-70)	59 (47-80)
Stroop Test B time (sec.)	before IFN-α+RBV	62 (53-66)	60 (45-65)	57 (50-68)
	after 3 mo IFN-α+RBV	65 (54-71)*	51 (40-63)	55 (48-65) ††
Stroop Test B (errors)	before IFN-α+RBV	5 (3-9)	4 (2-7)	3 (2-7)
	after 3 mo IFN-α+RBV	4 (3-6)	3 (2-4)	3 (1-5) ††

group 1 - patients with depressive symptomatology prior to treatment with IFN-α+RBV
group 2 - patients with depressive symptomatology after three-month treatment with IFN-α+RBV
group 3 - patients with no depressive symptoms
* - difference between group 1 and 2: $p<0.05$ (U test)
† - difference between before vs. after treatment, $p<0.05$ (Wilcoxon test)
†† - difference between before vs. after treatment, $p<0.01$ (Wilcoxon test)

Prevalence of depressive disorders among patients with hepatitis C who underwent IFN+RBV therapy in our study is similar to prevalence of these disorders in patients after stroke or patients with Alzheimer's disease [40, 41]. Since depressive symptoms are the most common signs accompanying therapy with interferon-α and ribavirine, it is obvious that they should be treated and evidence indicates that treatment with SSRI's is effective in majority of patients [19, 21]. In our study, patients who had depressive symptoms prior to therapy with IFN+RBV and were treated with an antidepressant for three months improved non-significantly in regard to depressive symptomatology at second assessment.

Older age predisposes depression [42, 43]. Age of the group with depressive symptomatology before IFN+RBV treatment was significantly older than age of the group with depressive symptoms induced by IFN+RBV therapy. Percentage of males and females in the latter group (25 patients) did not differ from the group of patients without depression (group 3). Female gender was significantly more prevalent among patients with depressive symptomatology before IFN+RBV initiation than both in patients with interferon-α induced depression and patients without depression. Female gender is a well-known risk factor for "regular" depression [44].

Severity of depression as rated with the HDRS was significantly greater after three month IFN+RBV therapy in group 2 than in the group of patients with depressive symptoms prior to therapy with IFN+RBV. This may be attributed to the institution of treatment with an antidepressant in patients of group 1 which brought about a non-significant decrease of depressive symptomatology.

Intensity of depressive symptoms grew remarkably also in patients with hepatitis C who did not have significant depression both at the

beginning of the study and after three month IFN+RBV therapy. On the other hand, performance on some neuropsychological tests in this group improved significantly after three month IFN+RBV treatment. The latter phenomenon has not been reported.

Depressive disorders are associated with a scope of cognitive dysfunctions. Attenuation of psychomotor speed, verbal fluency, attention, memory and executive functions in patients suffering from depressive disorders has already been described [45, 46, 47, 48]. On the other hand, cognitive dysfunctions commonly encountered in patients with hepatitis C are referred to as hepatic encephalopathy. It was demonstrated that the intensity of cognitive dysfunctions in patients with hepatitis C correlates with the degree of liver damage [2, 3, 4, 5, 6].

Data on the influence of therapy with interferon-α plus ribavirine on cognitive functions in patients with hepatitis C is limited. In a study of 56 patients with hepatitis C treated with interferon-α, MMSE decline (2-5 points) was detected after 2 and 4 weeks but it subsequently normalised [46]. Amodio et al. observed no changes in cognitive functions in 20 patients with hepatitis C treated for 6 months with interferon-α plus ribavirine and none of them had either depression prior to treatment, nor developed depression during IFN+RBV therapy [24]. Hilsabeck et al. compared cognitive functions of 11 patients treated for 6 months with IFN+RBV with 19 hepatitis C patients who were not treated. The former group performed significantly worse in the Trail Making Test B than the latter [50]. Kraus et al. examined 70 hepatitis C patients who underwent a 3 month IFN-α plus ribavirine therapy and revealed attention dysfunctions which were insignificantly correlated with the intensity of depressive symptoms [22]. On the other hand, in the study of Lieb et al. 38 patients with hepatitis B and C treated with interferon-α were prospectively observed for three months. Increasing of depressive symptoms as well as both verbal fluency decline and verbal memory impairment were observed after treatment with interferon-α. However, no correlations were found between depressive symptoms and verbal dysfunctions [51].

In our study, cognitive functions did not change due to IFN+RBV therapy in patients who had interferon-α induced depression. Patients who had significant depressive symptoms before IFN+RBV therapy had significantly worse verbal working memory after three month IFN+RBV treatment than patients who had interferon-α induced depression. This phenomenon has not been described.

Demographic and neuropsychological differences between groups compared in this study may suggest somewhat distinct pathophysiological mechanisms responsible for inducing depression by interferon-α than in the case of "standard" depression. In fact, preclinical and clinical data warrant such a hypothesis. Capuron and Miller proposed a model of interferon-α induced depression which consisted of two syndromes: mood/cognitive (associated with altered serotonin metabolism and responsiveness to antidepressants) and fatigue/psychomotor slowing (associated with altered dopamine metabolism and antidepressant non-responsiveness) [52]. Results of our study indicate that there are clinical and neuropsychological dissimilarities between "standard" and interferon-α-induced depression, however further research is needed to elucidate this issue.

CONCLUSIONS

Significant depressive symptoms were present in 18% patients with hepatitis C. Three-month treatment with interferon-α plus ribavirine (IFN+RBV) induced depressive symptoms in additional 25% patients with hepatitis C. The group of patients with depressive symptoms before IFN+RBV therapy was significantly older and female gender was remarkably more prevalent in comparison with the group of patients with depression induced by IFN+RBV therapy. Patients with depressive symptoms at enrolment exhibited significantly worse verbal working memory after three-month IFN+RBV therapy than patients with interferon-α induced depression and patients without depressive symptomatology both before and after IFN+RBV therapy exhibited significant improvement of psychomotor speed and verbal working memory after three-month IFN+RBV therapy. Clinical and neuropsychological differences may suggest distinct pathogenesis of standard and interferon-α induced depression.

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Recommendations of Prof. H. Kächele

PSYCHOANALYTIC INQUIRY Vol. 27 (2007) deals with the question: whether case reports should/can be written for research use?

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The case presentation is embedded in a theoretical discussion.

Thomä, H, H. Kächele. Comparative psychoanalysis on the basis of a new form of treatment reports. Psychoanalytic Inquiry, 2007, 27, 650—689.