Genotype 1 of hepatitis C virus increases the risk of major depression: a 12-week prospective study

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Abstract
Objective: Depressive symptoms have been frequently observed in association with immune activation. We prospectively evaluate depressive symptoms and risk factors for major depression in patients with hepatitis C virus treated with antiviral combined therapy.

Methods: Fifty patients were assessed during 1 year; the structured diagnostic interview — Mini International Neuropsychiatric Interview — was used to screen psychiatric disorders at the baseline and during the 4th and 12th week of antiviral therapy. Statistical analysis: generalized estimating equations and pairwise comparisons with Bonferroni adjustment.

Results: In our sample the prevalence of the Genotype 1 was 42%, and the pegylated interferon alpha plus ribavirin was the most prevalent treatment used for hepatitis C (86%). We found increased risk of depression in the 4th week (34%) but not in the 12th week (24%) compared with baseline values (20%) (P = 0.040). In addition, we found differences between baseline prevalence and hepatitis C genotypes, with higher odds in the 4th week compared to the baseline and 12th week (OR: 2.1 (1.15-2.9); P = 0.040). Patients with the Genotype 2/3 had significantly lower odds of presenting depression compared to the Genotype 1 (OR: 0.3 (0.1-0.9); P = 0.030).

Conclusion: This study provides evidence for an association between hepatitis C genotype and major depression, showing that besides immune activation, the Genotype 1 is associated with increased risk for psychiatric symptoms during the follow-up.

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1. Introduction

Nowadays, the hepatitis C virus (HCV) infects about 170 million people worldwide being the most frequent cause of chronic hepatitis and an important risk factor for liver cirrhosis and hepatocellular carcinoma [1]. Although most studies focus on the liver condition, the HCV infection can also lead to general health complications affecting other systems such as the cardiovascular and the central nervous system [2]. Preliminary studies show that HCV is possibly related to neurologic and psychiatric disorders [2], and higher prevalence of psychiatric comorbidities are frequently found in patients with chronic HCV infection [3,4]. Moreover, the treatment for HCV also increases the risk for psychiatric conditions, such as major depression [4].

Currently, the most commonly used treatment for HCV is the combined therapy with pegylated interferon alpha (PegIFN-α) and ribavirin (RBV) associated or not with protease inhibitors. Patients on interferon (IFN-α) treatment often experience side effects such as depressed mood, irritability, emotional lability, agitation, memory impairment and suicidal behavior [5–7]. In fact, IFN-α-based therapy has been associated to higher prevalence of depressive symptoms in HCV patients [8–10], especially during the first 12 weeks of treatment [5]. Depression by itself is not a contraindication for HCV treatment, although moderate to severe depressive symptoms are a common reason for postponing or excluding patients from antiviral therapy [6]. Therefore, a successful medical treatment of HCV requires detection and management of depressive symptoms at the baseline and during treatment [11].

The understanding of how different factors can affect the presence and severity of depression during HCV treatment might improve treatment compliance and patient’s quality of life. In HCV patients, the virus genotype is related to the severity of the liver condition, being reasonable to speculate that it might also play an important role in the psychiatric symptoms. The HCV genome is a positive-sense, single-stranded RNA genome approximately 10 kb long. The HCV genotypes are classified on the basis of the similarity of nucleotide sequence that is highly variable, with seven genotypes that are less than 72% identical at the nucleotide level [12]. Within the genotypes, subtypes with nucleotide identities of 75–86% may occur. Based on these genomic differences, genetic heterogeneity of HCV may account for some of the
differences in disease outcome and response to treatment observed in HCV-infected patients.

Indeed, the HCV Genotype 1 is considered the genotype with worst treatment response and disease prognosis [13,14]. In addition, Martin-Santos et al. showed that genotypes other than the Genotype 1 are related to higher odds of depression at the baseline [5]. Even though the antiviral therapy has evolved in the past years, showing better results for liver condition, the psychiatric side effects are poorly evaluated especially regarding the virus genotype.

Mental health problems during antiviral treatment have a strong impact on quality of life, reducing treatment compliance and are frequently associated with treatment failure [1,7]. Understanding the role of HCV genotype plays during treatment might be relevant to the development of new treatment protocols associated with a better management of depressive symptoms. Thus, the present study aims to investigate the effect of combined antiviral treatment for HCV (baseline, 4 weeks and 12 weeks) according to the virus genotype in the presence of major depression.

2. Methods

2.1. Sample and study design

This study is a convenience cohort where patients were followed up by 12 weeks during the antiviral therapy. The study was performed from February 2013 to March 2014, in the Ambulatório de Gastroenterologia — Centro de Aplicação e Monitoramento de Medicamentos Injetáveis — in Faculdade de Medicina da Universidade Federal de Pelotas (UFPel), Rio Grande do Sul, Brazil. The initial sample was composed of 55 HCV patients with treatment indication according to the Protocol Treatment of Viral Hepatitis of the Health Ministry [2011] [15]. We had five losses during the study development: two patients that did not start the use of medication due to clinical complications; two patients who refused to conduct the interviews in the 4th and 12th weeks; and one patient who discontinue treatment in the 4th week due to clinical complications related to pneumonia. Thus, 50 patients completed the 12 weeks of antiviral therapy. The health professionals who attend the service weekly monitored adherence to treatment through direct contact with the patients.

The treatment was based in drugs currently used for the HCV in Brazil. In our sample, 14% of the patients used the conventional IFN-α at a dose of 3 million/units three times a week, and 86% patients used PegIFN-α 2a at a dose of 180 mcg/kg once a week. These treatments were used in association with RBV (mean dose of 13 mg/kg/day) for 24 to 48 weeks depending on the virus genotype, viral load and fibrosis degree. The degree of fibrosis was assessed by the METAVIR System in which F0 means absence of fibrosis and F4 means cirrhotic patient. High viral load was defined by values above 600,000 IU/ml and low viral load by less than 600,000 IU/ml.

Psychiatric history was considered if the patient had previous episodes of depression or psychiatric treatment. Before starting treatment for HCV, 32% (16) of the patients used some type of psychiatric medication, and 52% (26) used psychiatric medication during the antiviral treatment.

2.2. Instruments

A sociodemographic questionnaire was applied at the baseline, before the beginning of the antiviral therapy. The psychiatric diagnostic interview and laboratory data of patients were collected at the baseline, the second interview occurred in the 4th week of treatment, and the last interview occurred in the 12th week of treatment.

Subjects were evaluated with a structured diagnostic interview — the Mini International Neuropsychiatric Interview — [16] that uses the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition [17] as criterion for psychiatric diagnostic. The diagnosis of major depression, risk of suicide and generalized anxiety disorder was used in the present work. The Beck Depression Inventory (BDI-II) interview was also used in order to assess the presence and severity of depressive symptoms in patients with HCV [18].

2.3. Laboratorial analysis

Laboratorial information such as the degree of fibrosis, virus genotype and viral load values were obtained from the UFPel Hospital along the antiviral therapy.

In our study, the prevalence of Genotype 1 was 42% (21), Genotype 2 was 18% (9), and Genotype 3 was 40% (20). Taking into account that Genotypes 2 and 3 have similar treatment indication for HCV and Genotype 1 demonstrates a worse disease prognosis as well as a poorer response to IFN-α treatment (14), all analysis were conducted considering the effects of Genotype 2/3 in relation to Genotype 1.

2.4. Statistical analysis

Sociodemographic and clinical characteristics of HCV patients were described by simple frequencies. Characteristics according to clinical diagnostic of major depression were compared by unpaired Student’s t-test or $\chi^2$, as appropriate. The prevalence of psychiatric diagnosis (depression as outcome) was compared with generalized estimating equations (GEEs) in time (baseline, 4th week and 12th week) and genotype (1 and 2/3) (working correlation matrix unstructured, scale response, binomial logit, main effect model). GEE analysis was performed using IFN-α treatment, antidepressant medication and prior history of major depression as covariates. In addition, pairwise comparisons with Bonferroni adjustment were conducted to identify differences between the prevalence of depression in different measures of time. Variables are presented as mean±standard deviation (SD) or percentage. The analyses were performed in SPSS 21.0 and P values <0.05 are considered statistically significant.

2.5. Ethical aspects

All ethical principles established by the National Health Council in Resolution No. 196 of 10 October 1996 were respected. All patients who agree to participate in the research provided a written informed consent. The study was approved by the University’s Ethics Committee (151.642). Any patient with a diagnosis of depression or suicide risk was referred to the Centro de Apoio Psicossocial (psychiatric service support to patients with mental disorders) or to the Psychiatric Service of UFPel.

3. Results

A total of 50 patients were included in this report. Table 1 describes the main characteristics of patients at baseline showing sociodemographic and clinical characteristics of the subjects. The gender was equally distributed ($P=0.832$), the average age was 51.7±12.5 years, 90% of the subjects were Caucasian and the prevalence of Genotype 1 for HCV was 42%. The most prevalent treatment for HCV was PegIFN-α associated with RBV (86%). Furthermore at baseline, 10 patients (20%) were in depressive episode, of which 9 (90%) remain depressive at 4th week and 6 (60%) at 12th week. During the follow-up, 8 patients (20%) developed depressive symptoms at 4th week and 5 (5%) at 12th week. Of all patients evaluated that developed depressive symptoms during the follow-up, 4 (40%) presented remission.

Sociodemographic and clinical characteristics according to major depression diagnosis were described in Table 2. No difference was observed between diagnosis and viral load before the beginning of the treatment ($P=0.136$), gender ($P=0.832$), fibrosis degree ($P=0.136$), HCV genotype ($P=0.170$), socioeconomic status ($P=0.835$), marital
status (P=1.000), work status (P=0.620) and years of study (P=0.493) (Table 2). Of all participants in this study, 24 (48%) had a prior history of major depression, and 9 (90%) of these patients with current depressive episodes in the pretreatment had a history of past depressive episodes (P=0.004).

During the treatment, the psychiatric comorbidities were evaluated showing that the HCV increased the risk of major depression after the 4th week (34%) and 12th week (24%) in comparison to the baseline (10%) (P=0.001; OR=2.3). However, the average BDI-II score was not different between the baseline (10.0±10.6), 4th week (12.5±12.6) and 12th week (11.4±10.2; P=0.230). The HCV treatment did not increase the risk for generalized anxiety disorder, with higher prevalence of anxiety in the baseline (26%) and 4th week of treatment (22%) in comparison to the 12th week of treatment (8%) (P=0.600). Suicide risk was not different in the 4th week (6%) and 12th (6%) when compared to baseline (10%) (P=0.530).

The present study also evaluated the influence of HCV genotype in the manifestation of depressive symptoms during treatment with IFN-α. We found significant differences between the prevalence of depression and the time of treatment with higher odds ratio in the 4th week compared to baseline and 12th week [OR: 2.1 (1.15–2.9); P=0.04] (Table 3). Also in Table 3, patients with HCV Genotype 2/3 had significantly lower odds ratio for the occurrence of depression when compared to Genotype 1 [OR: 0.3 (0.1–0.9); P=0.03]. Furthermore, after adjusting the GEE analysis for the use of antidepressant medication, IFN-α treatment and prior history of major depression, we found no significant effect for IFN treatment and antidepressant medication. The effect on the genotype was still significant (P=0.045), and the probability of developing depression during the treatment was 1.3 higher for Genotype 1 than for Genotype 2/3. In addition, the probability for participants that had prior major depression was more likely to develop depression during the study (P=0.001; OR=2.3).

4. Discussion

In this study, we showed that the prevalence of major depression and generalized anxiety disorder was higher in HCV patients when compared to literature data on general population [19,20]. According to literature, HCV patients are more frequently depressed than others [4], including hepatitis B chronic (HBV) infected patients, suggesting a specific association between HCV infection and the development of depression [20]. In addition, we found that patients with previous history of major depression had higher chances of recurrence during the antiviral treatment. Most studies show that previous history of depression is a risk factor for the development of psychiatric illness and depressive symptoms during the HCV treatment [1,5,21]. On the other hand, some inconsistent results were also reported in the literature [22]. Moreover, the high prevalence of previous depression in our sample can be related to the HCV infection prior to diagnosis of the disease.

The inflammatory hypothesis for depression was postulated more than two decades ago reinforcing the development of depressive states as a common side effect of IFN-α therapy [23]. Overall, the development of depressive symptoms during IFN-α treatment occurs in 30–70% of the patients [1,24,25]. However, this prevalence rate depends on the methods used for assessment (i.e., diagnostic interview, clinical evaluation, self-reports, observer-rated scales), the time of evaluation and the severity of depression. For instance, it is estimated that around 45–60% of the patients treated with IFN-α develops mild to moderate forms of depression and 15–40% develops moderate to severe depression [1,22,24,26].

It is believed that most of the adverse effects of IFN-α such as psychiatric comorbidities occur during the first 4th and 12th weeks after the beginning of the treatment [5,22,27,28]. Our study support increased frequencies of depression in the 4th week of IFN-α treatment when compared to baseline and 12th week [1,4,29,30]. In this context,
considering the great number of patients using psychiatric medication during the antiviral therapy, we can suggest that the higher prevalence of major depression observed in the 4th but not in 12th week may be due to the delay in the symptoms remission after antidepression treatment, since 52% of patients used psychiatric medication during the antiviral therapy [31]. Moreover, we failed to find changes in symptoms severity, suicide risk and generalized anxiety disorder during the HCV treatment.

The exact mechanism of PegIFN-α-induced depression is still unknown. Potential etiological factors may include (a) modulation of the serotonergic transmission, such as up regulation of serotonin uptake and transporter expression and serotonin receptor 1A activation [32]; (b) alteration of hypothalamic–pituitary–adrenal axis activity, associated with increased plasma cortisol levels and density of glucocorticoid receptors [33]; or (c) by induction of secondary cytokines, IL-1, IL-2, IL-6 and TNF-α [34]. In addition, functional neuroimaging studies with patients in PegIFN-α treatment showed decreased activity in the dorsolateral prefrontal cortex, similarly to depressive patients [35]. Recently, the IFN-α-induced increase in glutamatergic neurotransmission was also reported in dorsolateral prefrontal cortex and basal ganglia, suggesting that inflammatory cytokines may contribute to glutamatergic alterations in patients with mood disorders and increased inflammation [36].

Although both the treatment and the HCV virus might be related to increased prevalence of depression, we found a higher prevalence of major depression at the baseline (20%) regardless of treatment, supporting a possible effect of the HCV infection as previously shown in the literature [2]. In regard to the genotype and severity of the hepatic disease, studies have reported worse treatment response with PegIFN-α and RBV for patients infected with Genotype 1 of virus [37,38]. In fact, the Genotype 1 has been related to increased inflammatory activity and apoptotic mechanisms in the liver [37]. Therefore, one possible explanation for the relationship between Genotype 1 and psychiatric comorbidities is that HCV infection is a systemic condition capable to affect the CNS and not only the liver [2]. It is important for future studies to take into account broader effects of the infection and treatment response including psychiatric disorders.

The results presented here add to the literature data information about the HCV Genotype 1 for the psychiatric prognosis during IFN-α treatment. Genotyping HCV has been previously used as a tool for understanding the evolution and epidemiology of the virus and to determine the time and treatment prognostic [15]. However, little is known about the genotype influence in the manifestation of major depression, mainly due to the confounder factors associated to the depressive episode, such as history of past episodes, types of IFN-α and antidepressant medications. In fact, differently from our results, a previous report showed that genotypes other than Genotype 1 are related to higher odds of depression at baseline, but this effect do not seem to affect treatment [5]. It is important to mention that another study did not find an association between genotype and the prevalence of depression [11]. Those inconsistent results may be due to differences in genotype prevalence around the world.

In our study, some limitations should be taken into consideration: including the relatively small sample size and the use of psychiatric medication at baseline. It is important to mention that the sample size in our study may be a critical point for the lack of association between HCV genotype and depressive episode prior to 12th week. However, the identification of risk factors for mood and anxiety disorders associated to both HCV infection and treatment could help the development of psychotherapeutic support programs designed to increase adherence to antiviral therapy and improve the life quality of the patients.

5. Conclusions

This study provides evidence for an association between hepatitis C genotype and major depression, showing that besides immune activation, the Genotype 1 is associated with increased risk for psychiatric symptoms. Major depression in HCV patients influences their health-related quality of life and adherence to antiviral therapy, highlighting the importance of early recognition and treatment of interferon-induced depression. In general, the screening for depression in chronic HCV patients is not a routine practice due to time constraints or low ability to deal with psychological aspects of the disease. Depression inventories could help nonpsychiatric physicians to identify earlier symptoms of depression to reduce acute psychiatric complications and the need for pharmacological interventions during antiviral therapy. Moreover, more studies are needed to investigate the biological basis for the association between high prevalence of psychiatric disorders and the genotypes of HCV to better establish the per se virus effects.

Disclosures

The authors of this paper do not have any potential conflict of interests in connection with this manuscript.

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References


