

The Role of Attachment Style and Depression in Patients with Hepatitis C

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Abstract Patients infected with chronic hepatitis C virus (HCV) commonly suffer from the triad of depression, pain and fatigue. This symptom triad in HCV is likely influenced by additional psychological and interpersonal factors, although the relationship is not clearly understood. This retrospective study aimed to characterize the relationship between attachment style and depressive and physical symptoms in the HCV-infected population. Over 18 months, 99 consecutively referred HCV infected patients were assessed with the Hamilton Depression Rating Scale (HDRS), Fatigue Severity Scale, Patient Health

Questionnaire-15 for physical symptoms and the Relationship Questionnaire for attachment style. An ANOVA was used to identify differences between attachment styles and Pearson correlations were used to evaluate the association between depression, fatigue and physical symptoms. Approximately 15 % of patients in the sample had a fearful attachment style. Patients with fearful attachment style had significantly higher depressive symptoms compared to a secure attachment style ($p = .025$). No differences in physical and fatigue symptoms were observed between attachment styles. Further, HDRS scores were significantly associated with fatigue scores ($p < .001$) and physical symptoms ($p < .001$), reinforcing the relationship between these symptom domains in HCV-infected patients. Although depressive, physical and fatigue symptoms are inter-related in HCV-infected patients, our study results suggest that only depressive symptoms were influenced by the extremes of attachment style. Screening of relationship styles may identify at-risk HCV-infected individuals for depression who may have difficulty engaging in care and managing physical symptoms.

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Keywords Interpersonal relations · Depression ·
Hepatitis C · Social support · Fatigue

Introduction

Approximately 180 million individuals are infected with hepatitis C virus (HCV) worldwide (WHO, 1997) and the prevalence of HCV infection in the United States is ~1.6 % (Armstrong et al., 2006). Infection with hepatitis C (HCV) can result in significant impairment in health-related quality of life (HRQOL) (Bonkovsky & Woolley, 1999), can lead to social isolation and stigma for infected

individuals (Golden, Conroy, O'Dwyer, Golden, & Harouin, 2006) and is often coupled with high rates of depression and anxiety (El-Sarag, Kunik, Richardson, & Rabaneck, 2002). Moreover, chronic HCV is associated with significant physical complaints and symptoms (Kallman et al., 2007; Lang et al., 2006) with up to 70 % of HCV infected patients suffering from chronic pain diagnoses and fatigue (Barkhuizen et al., 1999; Whitehead et al., 2008).

Lifetime rates of depression range from 23 to 62 % in untreated HCV infected individuals (El-Sarag et al., 2002; Golden, O'Dwyer, & Conroy, 2005; Yovtcheva, Rifai, Moles, & Van der Linden, 2001) and current rates of depression are estimated at ~25–30 % (Golden et al., 2005; Yovtcheva et al., 2001). These rates of co-morbid depression in HCV-infected patients further complicate HCV treatment due to the preponderance of neuropsychiatric side effects of pegylated interferon-alpha (IFN α). IFN α -induced depression HCV occurs in nearly 25–30 % of HCV-infected patients (Horikawa, Yamazaki, Izumi, & Uchihara, 2003; Morasco et al., 2007) and may be associated with suicidal ideation if untreated (Dieperink et al., 2004; Sockalingam, Links, & Abbey, 2011). The presence of elevated depressive symptoms prior to initiating IFN α therapy is the most robust predictor of IFN α -induced depression (Lotrich, Rabinovitz, Gironda, & Pollock, 2007). Moreover, precipitating factors of depression in untreated and IFN α treated HCV patients are not well understood and require further exploration.

In HCV, depression is often associated with physical symptoms and fatigue. This symptom triad has been previously described in other chronic disease patient populations, such as in cancer and stroke (Kirkova et al., 2011; Naess, Lunde, & Brogger, 2012). In a study of 94 untreated HCV patients, Hilsabeck, Hassanein, Perry (2005) found that depression in association with poor social functioning, poor physical functioning and female gender, accounted for 68 % of the variance for fatigue. This symptom triad of depression, physical symptoms and fatigue are further exacerbated by HCV treatment with IFN α therapy (Majer et al., 2008; Raison et al., 2009). Several studies have demonstrated a relationship between pro-inflammatory cytokines activation and resulting phenomenon of “sickness behavior”, which includes symptoms of depression, lethargy, anorexia, hypersomnia, muscle and joint aches (Dantzer, 2009; Naess et al., 2012; Wichers et al., 2006). Treatment with IFN α has been shown to produce these proinflammatory states in patients and has been linked to IFN α -induced depression. Thus, there may be shared pathoetiology and high rates of co-occurrence amongst this symptom triad warranting further exploration.

Limited research has explored the role of social support and relationship style on this symptom triad in HCV and one

could argue that social support may be important to mitigating further psychosocial distress associated with these symptoms; however, some individuals have maladaptive relationship styles that may preclude their ability to tolerate psychosocial distress secondary to symptom triad burden, access social support, and cope with these symptoms in the context of chronic medical illnesses such as HCV infection (Hunter & Maunder, 2001). Relationship styles can be understood by way of attachment theory (Bowlby, 1969, 1973, 1980) which posits that the earliest bonds of children with their parents continue to impact social relationships throughout their life, resulting in persistent patterns of interpersonal interaction as adults, which are fairly static and highly stable over time (Waters, Hamilton, & Weinfield, 2000). This is a key element in understanding the reaction of patients to illness events, such as the diagnosis and treatment of HCV (Hunter & Maunder, 2001), and their ability to engage with HCV treatment teams.

Adult attachment styles can be divided into secure and insecure styles. The latter can be subdivided into preoccupied, dismissive and fearful styles. Secure attachment styles comprise 55 % of attachment styles in community samples (Mickelson, Kessler, & Shaver, 1997) and are characterized by the belief that other individuals are reliable and will act effectively in times of threat. Thus, securely attached individuals are likely to have moderate expression of affect and affect modulation (Hunter & Maunder, 2001). Individuals with insecure-preoccupied attachment styles are worried that other people do not care about them and interact on the premise that others will be helpful only if the communication of neediness is maintained. Preoccupied attachment styles occur in ~20 % of college age individuals (Mickelson et al., 1997) and are viewed by others as being “clingy”. Insecure-dismissive individuals are dismissive of the notion that other individuals are helpful during stress and operate under the assumption of “self-reliance is better than social support”. Dismissive attachment style has been observed within 15 % of the college aged cohort (Mickelson et al., 1997) and demonstrates high affect regulation and low emotional expression (Hunter & Maunder, 2001). Fearful attachment styles are characterized by high levels of avoidance and anxiety, which limit the ability of patients to use supports, and engage in treatment (Ciechanowski et al., 2004). Fearful attachment style has been observed in 22 % of HCV-infected individuals (Ciechanowski et al., 2004).

Studies have shown associations between fearful attachment style and depression (Meredith, Strong, & Feeney, 2006; Tremblay & Sullivan, 2010), higher recurrence and greater residual depressive symptoms, worse social functioning (Conradi & de Jonge, 2009), as well as a higher number of lifetime medically unexplained symptoms (Ciechanowski, Katon, Russo, & Dwight-Johnson,

2002a). This pathway to increased fatigue, depressive and physical symptom reporting, and the poor engagement in treatment can prove very challenging. As such, an understanding of attachment styles could facilitate identification of HCV-infected patients at an increased risk of worsening physical symptoms and psychological distress and provide clinicians with an approach to evaluating worsening physical symptoms and mood in the absence of clear physical or laboratory findings.

In an attempt to further characterize the impact of independent attachment styles on depressive, fatigue and physical symptoms in HCV-infected patients, we studied the differences between patients with secure attachment styles as compared to these with insecure attachment styles (preoccupied, dismissive and fearful relationship styles). We hypothesized that patients with a fearful attachment style (high anxiety and avoidance features) would report greater depressive, fatigue and physical symptoms. We also hypothesized that depressive, fatigue and physical symptom scores would be significantly correlated with each other.

Methods

Study Sample

This retrospective study included consecutively referred patients to the Hepatology and Mental Health Service at the University Health Network from a mixed secondary and tertiary referral based across Ontario between July 2009 and July 2010. Prior to undergoing a psychiatric assessment, a battery of psychological questionnaires was disseminated to a total of 123 patients by an administrative assistant. A total of 99 patients completed the entire questionnaire. The referral criteria for the Hepatology and Mental Health Service included any of the following: a past history of psychiatric illness, current treatment for a psychiatric illness and a positive screen on a self-report depression measure (Beck Depression Inventory (BDI) or Patient Health Questionnaire-9 (PHQ9) which were administered by Hepatology nurses) (Sockalingam et al., 2011).

The Hepatology and Mental Health Service provides integrated psychosocial assessment to patients being considered for HCV treatment with pegylated interferon- α (IFN α) and ribavirin. Patients in this study could be pre-, post- or currently receiving IFN α and ribavirin therapy. In this integrated program, patients with active depressive symptoms receive pharmacological and/or psychological treatment and only initiate HCV therapy when these symptoms have been stabilized. All patients who initiate HCV treatment are seen every 2 weeks for the first 12 weeks of treatment and monthly thereafter by a HCV treatment nurse trained to use self-report depression

screening measures (BDI or PHQ9). Some patients are concurrently followed every 2–4 weeks by a psychiatrist particularly if there are concerns about the stability of their psychiatric illness. Post-IFN α therapy patients consisted of patients who had failed IFN α therapy and these patients also receive psychiatric treatment until they are stabilized.

Inclusion criteria for this study included a positive quantitative RNA, age between 18 and 65 years and able to speak English. Patients who were currently encephalopathic as determined by the clinic psychiatrist were excluded from the study.

Procedures

All patients completed a series of self-report and clinician-rated scales. Only patients who had genotype 1 underwent a liver biopsy, which is congruent with routine clinical practice. A total of 99 patients were included in the final study sample and completed the study questionnaires. This study was approved by the Institutional Research Ethics Board at the University Health Network in Toronto, Canada.

Study Measures

Attachment style was assessed using the self-report Relationship Questionnaire (RQ) created by Griffin and Bartholomew (1994). The RQ categorizes patients into one of four attachment styles: secure, preoccupied, fearful and dismissive. Patients are required to choose from one of four statements that best described their predominant attachment style. Studies examining the RQ in college students (Bartholomew & Horowitz, 1991) and adults in romantic relationships (Griffin & Bartholomew, 1994) demonstrated both convergent and discriminant validity. The RQ has been used in large trials examining attachment styles in diabetic patients (Ciechanowski et al., 2010; Ciechanowski et al., 2006) and previously in a study of HCV-infected patients (Ciechanowski, Katon, Russo, & Dwight-Johnson, 2002a).

Each patient underwent a psychiatric assessment utilizing the 17-item Hamilton Depression Rating Scale (HDRS) to assess severity of depressive symptoms (Hamilton, 1960). HDRS scores of 0–7, 10–13, 14–17 and >17 correspond to normal range, mild depression, mild-moderate depression and moderate-severe depression. The HDRS was used based upon its previous use in HCV-infected patients (Morasco et al., 2007) and the potential advantage of clinician-rated scales over self-report measures (Sockalingam et al., 2011).

The Patient Health Questionnaire-15 (PHQ-15) is a measure of physical or symptoms traditionally used in patients suffering from functional disorders (Kroenke, Spitzer, & Williams, 2002); however, studies have utilized the PHQ-15 as a measure of physical symptoms (Hoge et al., 2008; Sha et al., 2005). Scores on the PHQ-15 range from

0 to 30 with higher scores indicating greater physical symptom burden. Physical symptoms listed on the PHQ-15 include headache, back pain and gastrointestinal symptoms.

The Fatigue Severity Scale (FSS) is a 9-item self-report scale for measuring fatigue and ranges for 0 to 63 with higher scores indicating greater fatigue (Krupp, LaRocca, Muir-Nash, & Steinberg, 1989). The FSS has been studied in HCV patients and has good internal consistency and test–retest reliability (Kleinman et al., 2000).

Liver biopsies were performed when clinically indicated and a total of 77 out of the 99 subjects (78 %) underwent a liver biopsy. Liver histology is reviewed within the institution by two dedicated liver pathologists, in a standardised and reproducible manner. Liver biopsy results were reported using Metavir fibrosis scores, with a score of 0 and a score of 4 representing no fibrosis and cirrhosis, respectively. The liver fibrosis score was included in our analysis for two reasons. First, rates of depression have ranged from 31 to 57 % in patients with liver cirrhosis and greater liver impairment has also been associated with increased depressive symptoms (Bianchi et al., 2005; Stewart, Enders, Mitchell, Felmlee-Devine, & Smith, 2011). Second, data has shown that general fatigue and physical symptoms can be more pronounced in patients with advanced liver disease (Kalaitzakis, Josefsson, Castedal, Henfridsson, & Bengtsson, 2012; Verne, Soldevia-Pico, Robinson, Spicer, & Reuben, 2004). The use of liver biopsy fibrosis scores was used to account for these potential confounding effects specifically on depression and physical symptoms.

Statistical Analysis

All statistical analysis was performed using SPSS 18.0. Descriptive statistics with means and standard deviations were reported for continuous variables. The statistical data met the assumptions of parametric analyses before statistical analyses were conducted. Normality of data was established for the HDRS, FSS and PHQ15 scores in our sample using the Kolmogorov–Smirnov test. Pearson correlations were used to analyze the association between HDRS, FSS and PHQ-15 scores. A one-way analysis of variance was conducted to compare mean scores on the HDRS, FSS, and PHQ-15 between the four relationship styles. Post hoc comparisons were conducted using a Tukey's test and statistical significance was defined as a $p < .05$.

Results

Participant Characteristics

The characteristics of 99 patients are summarized in Table 1. Approximately 62 % of our sample was male with

a mean age of 44.3 years. Over 80 % of HCV infected patients had genotype 1 and the mean liver fibrosis on liver biopsy for these patients was 2.2. The Metavir fibrosis scores [range is 0 (no fibrosis) to 4 (cirrhosis)] as per liver biopsy results in 77 patients who had HCV genotype 1 were not significantly different amongst the four attachment styles. At the time of this study, 21 % were receiving IFN α therapy and there was no statistically significant difference in the number of patients on IFN α therapy between the four attachment style groups. The distribution of attachment styles for the sample was as follows: secure (30 %), preoccupied (29 %), dismissive (25 %) and fearful (15 %). For all patients, the proportion with a past history of major depression did not differ amongst the four attachment style groups.

Association Between Depression and Physical Symptoms

Mean scores on the HDRS, FSS and PHQ-15 are reported in Table 1. Approximately 8 % of patients had moderate-severe depressive symptoms (defined as a HDRS score >17). Both untreated HCV infected patients and patients on IFN α therapy who had a past history of major depression had significantly higher depressive symptoms at the time of assessment (10.87 ± 5.94 vs. 7.83 ± 4.96 , $p = .007$); however, patients with a past history of depression did not have significantly higher moderate-severe depressive symptoms in comparison to those patients without a history of depression (5 vs. 3 %, $p = .469$). Correlations between

Table 1 Patient characteristics ($n = 99$)

Gender (male), n (%)	61 (62 %)
Age (years)	44.3 \pm 9.9
Genotype 1	83 (84 %)
Genotype 2	6 (6 %)
Genotype 3	8 (8 %)
Genotype 4	1 (1 %)
Genotype 5	1 (1 %)
Interferon-alpha treatment, n (%)	21 (21 %)
Fibrosis on liver biopsy* (mean \pm SD) ($n = 77$)	2.2 \pm 1.4
Biopsy proven cirrhosis	19 (19 %)
Relationship style, n (%)	
Secure	30 (30 %)
Preoccupied	29 (29 %)
Dismissive	25 (25 %)
Fearful	15 (15 %)
HDRS	9.3 \pm 5.6
FSS	42.6 \pm 15.2
PHQ-15	10.8 \pm 6.0

* ANOVA-no difference on liver biopsy fibrosis between attachment styles

Table 2 Correlation between depression and somatic measures

	HDRS	FSS	PHQ-15
HDRS	1	–	–
FSS	.447**	1	–
PHQ-15	.627**	.541**	1

** $p < .01$ **Table 3** Comparison between relationship styles

	Secure	Preoccupied	Dismissive	Fearful
HDRS	7.21 ± 4.6	3.81 ± .9	9.64 ± 6.4	11.34 ± 6.0*
FSS	41.10 ± 17.8	40.67 ± 15.2	39.82 ± 15.3	47.43 ± 11.4
PHQ-15	9.45 ± 5.2	11.67 ± 4.7	9.54 ± 5.7	12.89 ± 7.0

* Statistically significant difference compared to secure relationship style

HDRS, FSS, and PHQ-15 scores are outlined in Table 2. Depressive symptoms on the HDRS were strongly correlated with PHQ-15 scores ($r = .627$, $p < .001$) and moderately correlated with FSS scores ($r = .447$, $p < .001$). Age, gender and liver fibrosis were not significantly correlated with PHQ-15, FSS and HDRS scores.

Patients receiving IFN α therapy were compared with patients who were not (either pre- or post-IFN α therapy) and there was no significant difference in PHQ15 (12.32 ± 5.81 vs. 10.67 ± 6.47 , $p = .331$) and FSS (45.55 ± 13.11 vs. 41.28 ± 15.82 , $p = .285$) scores. There was a trend for higher HDRS scores for patients treated with IFN α (11.57 ± 6.92 vs. 8.96 ± 5.30 , $p = .084$), although this did not achieve significance (Table 3).

Differences in Depressive and Physical Symptoms Between Secure and Insecure Relationship Styles

No significant difference in FSS [$F(3, 95) = 1.39$, $p = .251$] and PHQ-15 [$F(3, 95) = 2.18$, $p = .095$] scores was observed between the four attachment styles using a one-way ANOVA; however, a significant difference in HDRS scores and attachment styles was found in the one-way ANOVA analysis [$F(3, 95) = 2.90$, $p = .039$]. Post hoc comparisons using Tukey's test revealed a significant difference between the mean scores for secure ($M = 7.21$, $SD = 4.63$) and fearful ($M = 11.34$, $SD = 6.00$) but not with dismissive ($M = 9.64$, $SD = 6.43$) and preoccupied ($M = 8.53$, $SD = 3.81$) attachment styles. No difference was observed for HDRS scores between the 3 insecure attachment styles.

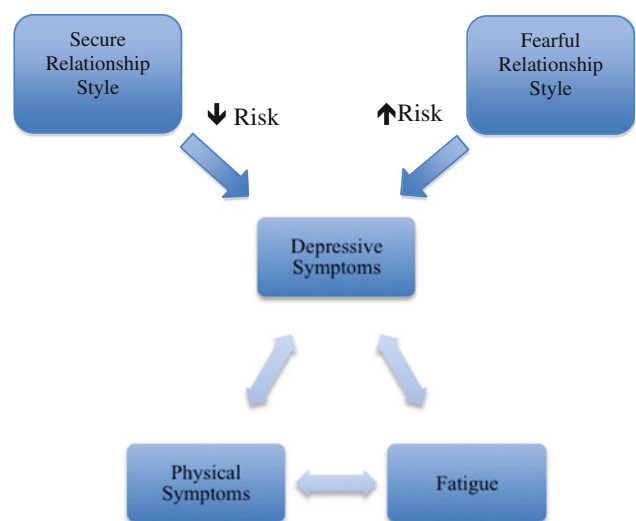
Discussion

The purpose of this study was to examine the effect of insecure attachment styles in HCV patients on physical, fatigue and mood symptoms. The distribution of attachment styles in our sample of HCV patients closely resembled the distribution of attachment styles observed by Ciechanowski and colleagues (2002a) in their sample of 32 HCV-infected patients.

Our study results suggest that attachment style may be a risk factor for depressive symptoms in HCV, which could have downstream effects on physical symptoms and fatigue (see Fig. 1). Patients with fearful attachment styles had significantly higher depressive symptoms compared to patients with a secure attachment style. The HDRS scores for patients with fearful attachment style exceeded the clinical threshold for depression (mild depressive symptoms) where as securely attached patients had depression scores in the “no depression” range as per the HDRS. This finding parallels previous studies reporting greater vulnerability to depressive symptomatology with this attachment style (Ciechanowski, Walker, Katon, Korff, & Simon, 2002b; Conradi & de Jonge, 2009).

Fearful attachment style may also contribute to the engagement of HCV-infected patients with healthcare providers for assessment of HCV and potential treatment. The effects of fearful attachment style on depression in HCV could be due to poor access to depression treatment due to maladaptive interpersonal style and further perceived isolation secondary to the stigma of HCV (Golden et al., 2006).

Our study results should be considered with acknowledgement of potential limitations. First, our study sample

**Fig. 1** Model for understanding relationship style, depressive symptoms and somatic symptoms in HCV

may not be generalizable to all patients with HCV, as patients in the study were referred to an integrated psychiatry service within the Hepatology Clinic at a secondary and tertiary care center. Moreover, these results may not be applicable to patients infected with HCV who do not come to care, although it is possible that this patient sub-group could have higher rates of fearful attachment style. In addition, attachment style did not appear to have direct effects on fatigue and physical symptoms in this sample of patients with moderate liver disease and it is possible that the PHQ-15 was not sensitive enough to detect differences in somatic symptoms between the different attachment style groups. We had fewer patients on IFN α therapy in our sample and although IFN α treatment did not significantly increase depressive, physical and fatigue scores, treatment status may have been a confounding variable limiting our results.

Moreover, our study sample size may not have been adequately powered to detect a difference, as convenience sampling was employed based upon the limited literature in this area. The moderate level of fibrosis in most of our sample may have also limited our ability to discern the differences in fatigue and physical symptoms between attachment styles, as compared to a patient sample with minimal fibrosis secondary to HCV. It should be noted that markers of liver disease severity were not reported in the previous study showing a relationship between fearful attachment style and medically unexplained symptoms in HCV-infected patients (Ciechanowski et al., 2002a).

It is important to recognize that in the midst of illness, such as HCV, patients will often experience healthcare providers as attachment figures. Therefore, attachment style will influence their interactions with clinicians in this context and could be a contributing factor to the 41 % of HCV-infected patients reporting communication difficulties with their physician (Zickmund et al., 2006). Moreover, healthcare providers have also experienced “difficulties” with patient encounters due to patients’ insecure attachment styles, which may influence the ability to establish a therapeutic working relationship (Maunder et al., 2006). For example, a patient with a fearful attachment style may be more likely to flee once a level of perceived closeness is experienced. Moreover, fearful attachment style patients may desire social contact but may at the same time be inhibited by a fear that they will be rejected. Since fearful attachment styles are stable patterns of interrelatedness, the involvement of a mental health care professional during the assessment and treatment of these patients may assist with patients’ treatment engagement with the medical team and alleviate psychological distress.

It may be beneficial to consider attachment style when assessing patients with HCV, as it may inform the ability to engage patients in treatment relationships and also may provide some insight into potential vulnerability for mood

symptoms. Further research is needed to determine if attachment style stratification can predict HCV treatment outcomes, neuropsychiatric side effects and sustained virological response following IFN α therapy.

Conflicts of interest The authors have no conflicts of interest to disclose.

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