Published in final edited form as:
J Affect Disord. 2009 December ; 119(1-3): 181–185. doi:10.1016/j.jad.2009.02.017.

Does Cytokine-Induced Depression Differ from Idiopathic Major Depression in Medically Healthy Individuals?

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Abstract

Background—Cytokines of the innate immune response may contribute to behavioral alterations that resemble major depression as manifested in medically healthy individuals.

Methods—To explore potential similarities and differences between cytokine-induced depression and idiopathic major depression in healthy subjects, dimensional analyses comparing specific symptom dimensions of depression were conducted in 20 patients with malignant melanoma administered the innate immune cytokine, interferon (IFN)-alpha, and 28 medically healthy subjects

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Conflict of Interest: Dr. Miller has served as a consultant for Schering Plough and AstraZeneca and has received grant support from GlaxoSmithKline, Janssen and Centocor. Dr. Harvey has served as a consultant for Eli Lilly, Johnson and Johnson, Merck and Company, Pfizer, Inc, Novartis Pharma, Solvay-Wyeth, and Dainippon Sumitomo America, Inc. He has current grant support from Astra-Zeneca. Dr. Ninan is an employee of Wyeth Pharmaceuticals. All other authors declare they have no conflicts of interest.

Contributors: Dr. Capuron was responsible for the study design, statistical analyses, and preparation of the manuscript. Ms. Fornwalt was responsible for data collection and management, statistical analyses, and manuscript preparation. Ms. Knight was responsible for patient recruitment, psychiatric assessment, data collection, and data management. Dr. Hravey was responsible for statistical analysis, data interpretation and manuscript preparation. Dr. Ninan was responsible for study design, psychiatric assessment, and data interpretation. Dr. Miller was responsible for study design, statistical analyses and manuscript preparation. All authors contributed to and approved the final manuscript.

with major depression of similar age and gender distribution. The Hamilton Rating Scale for Depression was used to assess severity of individual depressive symptoms.

Results—Severity of symptoms of anxiety, depressed mood, and impaired work/activities were comparable between patients with IFN-alpha-induced depression and medically healthy depressed patients. Interestingly, however, compared to medically healthy patients with major depression, patients with IFN-alpha-induced depression reported significantly greater psychomotor retardation and weight loss and significantly less severe feelings of guilt.

Limitations—The relatively small sample size limited statistical power to detect small differences in symptom expression among groups.

Conclusions—The data suggest that there is considerable overlap in symptom expression between cytokine-induced depression and idiopathic depression in medically healthy subjects. Nevertheless, differences in isolated symptom domains suggest that cytokines may preferentially target neurocircuits relevant to psychomotor activity (e.g. basal ganglia), while having a limited effect on cognitive distortions regarding self-appraisal.

Keywords

Depression; Cytokine; Interferon-alpha; Psychomotor Slowing; Guilt

INTRODUCTION

Recent theories have proposed that immune factors, notably innate immune cytokines, may contribute to the development of depression in medically ill and possibly medically healthy populations. In support of this hypothesis, data have shown that innate immune cytokines can influence virtually every pathophysiologic domain relevant to depression including neurotransmitter metabolism, neuroendocrine function, regional brain activity and, ultimately, behavior (Dantzer et al., 2008; Raison et al., 2006). Behavioral changes related to activation of innate immune responses include depressed mood, anhedonia, cognitive dysfunction, anxiety, psychomotor slowing, fatigue, anorexia, sleep alterations, and increased sensitivity to pain (Capuron et al., 2002; Capuron and Miller 2004; Dantzer et al., 2008). These symptoms closely resemble those of major depression, and evidence for a connection between activation of the innate immune response and depression has been found in a number of studies [see for review, (Anisman et al., 2005; Dantzer et al., 2008; Raison et al., 2006). For example, increased peripheral blood concentrations of acute phase proteins, chemokines and adhesion molecules as well as increased blood and cerebrospinal fluid concentrations of innate immune cytokines and their soluble receptors have been reported in medically ill as well as medically healthy patients with major depression (Raison et al., 2006). Moreover, administration of innate immune cytokines [e.g. tumor necrosis factor (TNF)-alpha, interleukin (IL)-1, and IL-6] or agents (e.g., lipopolysaccharide or typhoid vaccination) that stimulate an innate immune response have been found to induce depressive-like behaviors in laboratory animals and humans (Brydon et al., 2008; Dantzer et al., 2008; Raison et al., 2006; Reichenberg et al., 2001; Yirmiya, 1996). Finally, inhibition of cytokines and their signaling pathways has been associated with improved mood and increased responsiveness to conventional antidepressant medications (Muller et al., 2006; Tyring et al., 2006).

To further explore the relationship between cytokines and depression, a number of investigators have examined patients undergoing treatment with the innate immune cytokine, interferon (IFN)-alpha, for viral infections and cancer (Capuron and Miller 2004; Musselman et al., 2001). Although an effective therapy, IFN-alpha causes significant depressive symptoms, with up to 50% of patients meeting DSM-IV symptom criteria for major depression, depending on the dose (Capuron and Miller 2004; Musselman et al., 2001). Interestingly, no study has directly

compared relevant symptom domains in patients with IFN-alpha-induced depression versus idiopathic depression that occurs in ostensibly medically healthy individuals. Therefore, we endeavored to compare the depressive syndrome induced by IFN-alpha to major depression in medically healthy subjects using an analysis of relevant symptom dimensions.

METHODS

Patients

All patients provided written informed consent prior to study participation, and all study procedures were *a priori* approved by the Emory University Institutional Review Board.

Medically ill patients treated with IFN-alpha—Twenty patients (10 males, 10 females, mean age: 50.3 years, range: 25-74 years) with malignant melanoma were included in the study. Patients had been surgically rendered clinically free of disease and were receiving high-dose IFN-alpha therapy (Intron A) for stage II-IV malignant melanoma with a 50% or greater risk of recurrence. The IFN-alpha treatment regimen involved 20 million international units (MIU) per square meter of body surface area five days per week for the first four weeks of therapy, followed by 10 MIU/m^2 administered subcutaneously three days per week. Medical exclusion criteria included unstable cardiovascular, endocrine, hematological, hepatic, renal or neurologic disease as determined by medical history, physical examination and laboratory testing. Psychiatric exclusion criteria included a past or current diagnosis of schizophrenia or bipolar disorder or a current diagnosis of major depression or substance-related disorder prior to IFN-alpha administration as assessed by the Structured Clinical Interview for Diagnostic and Statistical Manual (DSM) IV Axis I disorders (SCID) (Association, 1994). Patients receiving active treatment with antipsychotic and/or antidepressant medications or mood stabilizers at any point during the study were also excluded. Past history of psychotropic medication usage and current or past participation in psychotherapy and/or counseling were not routinely assessed and were therefore not used to exclude or otherwise categorize IFN-alpha-treated subjects. Five IFN-alpha-treated patients had a past history of depression including 4 patients with major depression and 1 patient with dysthymic disorder. Although anxiety disorders including generalized anxiety disorder, panic disorder, post traumatic stress disorder and phobia were not exclusionary, no patients received an anxiety disorder diagnosis prior to IFN-alpha treatment. All patients were recruited from the Winship Cancer Institute of the Emory University School of Medicine and represent a subset of patients described previously (Capuron et al., 2002; Musselman et al., 2001). Patients were followed during the first twelve weeks of IFN-alpha therapy with neuropsychiatric assessments occurring on a weekly basis during the first 4 weeks of treatment and every four weeks thereafter.

Medically Healthy Depressed Patients—Twenty-eight medically healthy patients (11 males, 17 females, mean age: 50.7, age range: 40-62) with a current diagnosis of major depression as determined by the SCID were enrolled in the study. These patients were recruited from the Mood and Anxiety Disorders Program at the Emory University School of Medicine. Patients with certain co-morbid DSM-IV disorders [i.e. current major depression with antecedent dysthymic disorder, chronic major depression (duration greater than 2 years), or recurrent major depression with incomplete recovery between episodes] were included, provided that major depression was the primary DSM-IV diagnosis. Patients with diagnoses of past or current schizophrenia or bipolar disorder or a primary diagnosis of post traumatic stress disorder, obsessive compulsive disorder, alcohol dependence/abuse disorder, or substance dependence/abuse disorder within the past year were excluded, as were patients on psychotropic medications or with significant or unstable medical illness as determined by medical history, physical examination and laboratory testing.

Assessments

Depressive symptoms were assessed by a trained clinician using the 17-item Hamilton Rating Scale for Depression (HAM-D), an observer-administered instrument containing questions rated from 0 (absent) to 4 (severe) (Hamilton, 1960).

Data Analysis and Statistics

Demographics variables were compared among groups using either T-test or chi-square statistics. Multivariate analysis of variance (MANOVA) was used to compare differences in HAM-D items among IFN-alpha-treated patients with major depression, IFN-alpha-treated patients without major depression, and medically healthy patient with major depression. Simple main effects and post-hoc comparisons (Tukey) were performed for individual items where indicated. In patients with IFN-alpha-induced major depression, scores on the HAM-D were obtained at the time of maximum severity of depression as defined as the visit with the highest score on the depressed mood item on the HAM-D. Time of maximum depression occurred after an average of 7 ± 3 (standard deviation) weeks of IFN-alpha treatment, and therefore scores were compared to HAM-D scores obtained at 8 weeks for non-depressed IFN-alpha-treated subjects. HAM-D scores in medically healthy depressed participants were obtained once during an episode of active illness at baseline prior to enrollment into a clinical research study.

RESULTS

There were no significant differences in age ($t(46) = 0.13$, $p = 0.90$) or gender ($Chi^2(1) = 0.54$, $p = 0.46$) between patients treated with IFN-alpha and medically healthy depressed patients. As reported elsewhere (Capuron et al., 2002; Musselman et al., 2001), 9 patients with malignant melanoma developed symptoms sufficient to meet criteria for major depression (according to DSM-IV) during treatment with IFN-alpha, and 11 remained free of depression. No significant differences between patients with IFN-alpha-induced depression (5 males, 4 females, mean age: 56 years, range: 44-74 years) and medically healthy depressed patients were found, although the IFN-alpha-treated depressed group was slightly older (age: $t(35) = 1.88$, $p = 0.07$; gender ($Chi^2(1) = 0.73$, $p = 0.39$)

The expression of specific symptom dimensions was compared among groups using MANOVA. Results indicated a significant effect of group [$F(2,45)=26.53$, $p<0.0001$], item [$F(16,720)=25.93$, $p<0.0001$] and a significant group X item interaction [$F(32,720)=5.26$, $p<0.0001$]. Simple main effects and post-hoc comparisons revealed group differences primarily for the dimensions of depressive symptoms, anxiety symptoms, impaired activity/decreased tone and weight loss (see Table 1). As indicated in Table 1, compared to IFN-alpha-treated non-depressed patients, both patients with IFN-alpha-induced depression and medically healthy patients with major depression exhibited significantly higher scores on items measuring depressed mood (both $p<0.001$), anxiety ($p<0.001$ and $p<0.01$, respectively), hypochondriasis ($p<0.05$ and $p<0.01$, respectively) and impaired work/activities (both $p<0.001$). Moreover, medically healthy depressed patients exhibited greater scores in feelings of guilt and suicidal thoughts as well as agitation when compared to IFN-alpha-treated non-depressed patients. Retardation scores (thought, speech, concentration, and motor activity) were greater in patients with IFN-alpha-induced depression in comparison to both IFN-alpha-treated non-depressed subjects ($p<0.05$) and medically healthy depressed patients ($p<0.05$). Similarly, reported loss of weight was significantly higher in patients with IFN-alpha-induced depression compared to medically healthy depressed patients ($p<0.05$). In contrast, feelings of guilt were significantly higher in medically healthy patients with depression versus both patients with IFN-alpha-induced depression and non-depressed IFN-alpha-treated subjects ($p<0.001$).

DISCUSSION

The present data suggest that there is a considerable overlap between the behavioral syndrome caused by innate immune cytokines and DSM-IV idiopathic major depression in otherwise healthy individuals. This overlap was apparent in most prominent dimensions of depression, including depressive symptoms, anxiety symptoms and impaired activity. However, in comparison to medically healthy depressed patients and IFN-alpha-treated non-depressed subjects, patients with IFN-alpha-induced depression exhibited significantly greater symptoms of psychomotor retardation and reported weight loss, suggesting that these symptoms may be preferentially expressed in the cytokine-induced depressive syndrome. In contrast, patients with IFN-alpha-induced depression expressed significantly less severe feelings of guilt.

The greater prominence of psychomotor retardation in IFN-alpha-treated patients is consistent with two studies documenting motor slowing during IFN-alpha therapy using computerized neuropsychological testing. In addition, treatment of rhesus monkeys with IFN-alpha was associated with reduced locomotor activity in subordinate animals (Capuron et al., 2001; Felger et al., 2007; Majer et al., 2008). IFN-alpha-induced motor slowing has in turn been associated with the development of depression and fatigue in patients with cancer and infectious disease (hepatitis C) (Capuron et al., 2001; Majer et al., 2008). Given the role of the basal ganglia in regulating motor activity, these data are compatible with altered glucose metabolism in basal ganglia nuclei (putamen, globus pallidus and nucleus accumbens) of IFN-alpha-treated subjects as measured by positron emission tomography (Capuron et al., 2007; Juengling et al., 2000). Of note, administration of typhoid vaccination has also been shown to lead to psychomotor slowing associated with altered activation patterns in the basal ganglia (substantia nigra) as assessed by functional magnetic resonance imaging (Brydon et al., 2008). Taken together, these data suggest that immune activation and innate immune cytokines such as IFN-alpha may target the basal ganglia, leading to alterations in psychomotor speed.

Patients with IFN-alpha-induced depression also reported higher levels of weight loss, likely due to the anorectic effects of this and other cytokines (Plata-Salaman, 1996; Plata-Salaman, 1998). This possibility is supported in part by the lack of difference in scores of reported weight loss between patients with IFN-alpha-induced depression and IFN-alpha-treated non-depressed subjects, indicating an impact on reported weight across IFN-alpha treatment irrespective of the development of depression. Moreover, GI symptoms (which largely refer to appetite) were slightly, although not significantly, higher in IFN-alpha-treated subjects.

Interestingly, general somatic symptoms (which largely refer to muscle aches and fatigue) were increased to a comparable degree in all groups. Somatic symptoms are not surprising in IFN-alpha-treated patients. Nevertheless, the presence of physical symptoms in medically healthy individuals is consistent with previous studies on co-morbid physical complaints in ostensibly medically healthy depressed patients (Bair et al., 2003; Kroenke et al., 1997; Simon et al., 1999).

The absence of symptoms of excessive guilt in IFN-alpha-treated patients is noteworthy and similar to what has been recently reported in patients who developed depression following bereavement (Kendler et al., 2008). The absence of guilt under these circumstances of depression may reflect, in part, the sense of IFN-alpha-treated (and bereaved individuals) that the source of emotional distress is outside their locus of control (Kendler et al., 2008). In addition, it is possible that the relatively delimited exposure to IFN-alpha-induced depression may obviate the psychological consequences of long-term depression exposure, which may impinge upon more endearing aspects of self-appraisal including affective/cognitive distortions such as low-self esteem and high self-criticism. Of relevance in this regard is the possibility that the expression of depressive symptoms in the later stages of IFN-alpha therapy

(i.e. after 12 weeks) may differ from that early in treatment. Because IFN-alpha-treated patients were not examined after 12 weeks, it remains possible that chronic exposure to cytokine therapy may eventually influence aspects of psychological function including self esteem and guilt.

Limitations of the study include the relatively small sample of subjects with IFN-alpha-induced depression. Given the sample size of the study, power calculations revealed a 99% power to detect a 1 point difference between groups in individual items on the HAM-D, an 83% power for the detection of a 0.5 point difference and 30% power to detect a 0.25 point difference (Cohen, 1988). Nevertheless, the clinical relevance of small differences (below 0.5 points) in symptom severity is unclear. Moreover, the differences that were detected represent large effect sizes between groups which likely reflect true differences in the expression of relevant symptoms.

In sum, findings from the present study indicate a high degree of overlap between idiopathic major depression in healthy subjects and IFN-alpha-induced depression. These data are consistent with the capacity of innate immune cytokines to interact with multiple pathophysiologic pathways known to be involved in depression. Moreover, given the prominence of psychomotor retardation in the context of IFN-alpha (and other immune stimuli), consideration should be given to the notion that cytokines may preferentially target basal ganglia circuitry with related implications for other neurovegetative functions including anhedonia and fatigue as well as dopamine metabolism. Finally, increased feelings of guilt in idiopathic major depression, suggest that such cognitive-affective symptoms may be a consequence of chronic depressive illness or may represent a psychological (or characterologic) vulnerability factor for the disease.

Acknowledgments

The authors would like to thank Drs. Dominique Musselman, Jane Gumnick and Marina Demetrashvili for conducting patient interviews and Ms. Bobbi Woolwine for supervising data collection from the medically healthy depressed subjects.

Role of Funding Source: Funding for this study was provided in part by NIMH Grants MH00680 and MH60723. The NIMH had no further role in study design; in the collection, analysis and interpretation of data; in the writing of the report; and in the decision to submit the paper for publication.

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Table 1

Mean (±SD) depressive symptom severity as measured by the HAM-D scale in medically healthy depressed patients (n=28), patients with IFN-alpha-induced depression (n=9) and IFN-alpha-treated non-depressed patients (n=11)

	IFN-alpha-treated Non-Depressed Patients (n=11)	IFN-alpha-treated Depressed Patients (n=9)	Medically Healthy Depressed Patients (n=28)
Depressive Symptoms			
Depressed mood	0.36 (.92)	3.00 (.71)***	2.50 (.58)***
Feelings of guilt	0.09 (.30)	0.22 (.67)	1.50 (.51)*** ‡
Suicide	0.18 (.60)	0.78 (.97)	1.18 (.77)**
Anxiety Symptoms			
Anxiety psychic	0.46 (.69)	1.78 (1.48)**	1.86 (.71)***
Hypochondriasis	0.27 (.47)	1.44 (1.13)**	1.00 (.82)*
Agitation	0.09 (.30)	0.78 (1.09)	0.89 (.63)**
Anxiety somatic	1.27 (1.0)	1.78 (.97)	1.71 (.81)
Impaired Activity/Decreased Tone			
Work/activities	1.18 (1.1)	3.00 (.71)***	2.61 (.57)***
Retardation	0.27 (.65)	1.22 (1.20)*	0.39 (.69) #
Sleep Alterations			
Insomnia early	0.36 (.67)	0.56 (.88)	1.00 (.94)
Insomnia middle	0.55 (.82)	1.00 (.87)	1.18 (.72)
Insomnia late	0.46 (.82)	0.89 (.93)	0.86 (.70)
Somatic Symptoms			
Somatic symptoms GI	0.64 (.81)	0.78 (.67)	0.46 (.58)
Somatic symptoms general	1.64 (.67)	1.78 (.44)	1.89 (.31)
Genital symptoms	0.55 (.82)	1.22 (.83)	1.11 (.83)
Loss of weight	0.73 (1.0)	1.00 (1.0)	0.18 (.48) #
Other			
Insight	0.09 (.30)	0.11 (.33)	0.07 (.38)
Total HAM-D Score	9.18 (5.98)	21.33 (6.44)***	20.39 (3.08)***

Higher scores represent greater symptom severity.

Between groups comparisons:

* p<0.05;

** p<0.01;

*** p<0.001 compared to IFN-alpha-treated non-depressed subjects;

# p<0.05,

† p<0.01;

‡ p<0.001 compared to IFN-alpha-treated depressed patients.

Abbreviations: SD- standard deviation; HAM-D- Hamilton Rating Scale for Depression; IFN-interferon; GI-gastrointestinal