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Associations between immune activation and the current severity of the "with anxious distress" specifier in patients with depressive disorders

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ABSTRACT

Objective: Immune dysregulation may be linked with depressive disorders and in particular anxiety symptoms. This study compared the levels of immune factors, demographic and clinical characteristics of patients with depressive disorders between mild to moderate and moderate–severe to severe anxious distress groups.
Methods: This study included 177 patients diagnosed with a depressive disorder who were hospitalized between March 2012 and April 2015. The patients were categorized into mild to moderate and moderate–severe to severe anxious distress groups, based on the Hamilton Depression Rating Scale (HAM-D) scores on the Agitation and Anxiety–Psychic subscales. The charts of the patients were reviewed to evaluate immune factors, including C-reactive protein (CRP) and white blood cell levels, confounding factors, such as smoking, other general medical disorders and body mass index, and demographic and clinical characteristics, such as age, sex, total HAM-D scores, comorbidities, family history of mood disorders, suicidality, psychotic features and prescription patterns.
Results: The moderate–severe to severe group tended to have higher CRP and monocyte levels compared with the mild to moderate group. After adjusting for the HAM-D scores, patients with moderate–severe to severe anxious distress had a significantly greater trend toward significance for suicidality and a higher rate of antipsychotic use.
Conclusion: High levels of anxiety symptoms may modulate the inflammatory response and course of illness, affecting treatment planning.

1. Introduction

The *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (*DSM-5*) includes the new specifier "with anxious distress," which refers to high levels of anxiety symptoms that exist as a prominent feature in both patients with bipolar disorder and patients with major depressive disorder (MDD) in primary care and specialty mental health settings [1]. Four of the five symptoms (feeling keyed up or tense, feeling unusually restless, difficulty concentrating because of worry and fear that something awful may happen) overlap with symptoms that are used to diagnose generalized anxiety disorder (GAD), while the remaining symptom (feeling that the individual might lose control of himself or herself) is related more to panic disorder [2]. This suggests that a majority of patients who experience mood episodes in conjunction with serious anxiety and motor agitation symptoms should be specified using this criterion.

This newly added specifier is associated with various backgrounds and literature references in both clinical and research settings. The presence and severity of anxiety symptoms in patients with mood episodes affect illness severity and duration, family history, treatment response, and suicidality [3]. Studies using the *DSM-5* criteria have revealed that anxious distress in patients with mood disorders is associated with a higher risk of suicide, longer duration of illness and greater likelihood of a lack of response to treatment [1]. Severe anxiety occurs frequently in patients with depressive disorders and is clearly associated with more severe depressive symptoms, greater functional impairment, poorer short- and long-term outcomes and higher rates of help seeking for both psychological and medical problems [4–6].

However, the pathophysiology of severe anxiety or psychomotor agitation in depressive disorder remains to be clarified. Immune dysregulation, and increased inflammation in particular, is a possible pathological mechanism involved with depressive disorders that has been investigated by many researchers [7]. It has been demonstrated that genetic variants influence the biological mechanisms by which the innate immune system contributes to the development of depression [8]. This immune dysregulation hypothesis has also has been implicated in anxiety disorders [9]. The relationships among various immune factors and severe anxiety or psychomotor agitation, which is

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one of the most important clinical components of anxiety that can influence the course and prognosis of a depressive disorder, remain to be clarified.

Therefore, the aim of the present study was to evaluate relationships between immune factors and severe anxiety or psychomotor agitation in depressive disorder. This study compared the immune factors, specifically C-reactive protein (CRP) levels and white blood cell (WBC; neutrophils, lymphocytes and monocytes) counts, of subjects with varying degrees of unipolar depressive disorder as a primary measure. In addition, as secondary measures, the demographic data and clinical characteristics of the patients, as well as other possible confounding variables that may have contributed to changes in the levels of immune factors, were compared between patients with mild to moderate and moderate–severe to severe anxious distress. All patients were diagnosed with unipolar depressive disorder based on the diagnostic and statistical manual of mental disorders, 4th edition, text revision *(DSM-IV-TR)* and *DSM-5* and then classified with either "mild to moderate" or "moderate–severe to severe" anxious distress based on the Agitation and Anxiety–Psychic subscales of the 17-item Hamilton Rating Scale for Depression (HAM-D), which was performed at the initial hospitalization.

2. Methods

2.1. Patients

The medical charts of the patients included in this study were reviewed retrospectively. All participating patients were diagnosed by a board-certified psychiatrist using a clinical interview in accordance with the *DSM-IV-TR* and *DSM-5* criteria for unipolar depressive disorders between March 2012 and April 2015 at St. Mary's Hospital, College of Medicine at The Catholic University of Korea in Seoul, Korea. The inclusion criteria for the study were as follows: (a) a current diagnosis of unipolar depressive disorder based on the *DSM-IV-TR* and *DSM-5* criteria; (b) HAM-D data from the initial hospitalization; and (c) initial CRP levels and WBC counts, including neutrophils, lymphocytes and monocytes. The exclusion criteria were insufficient data (missing HAM-D values, confounding variables such as smoking, other medical disease, height, weight and laboratory data), a severe comorbid medical or neurological condition that could contribute to depressive symptoms, the recent onset of an organic brain lesion that could influence depressive symptoms and a thought disorder such as schizophrenia or a schizoaffective disorder. However, mild or chronic medical conditions such as hypertension, diabetes mellitus, hyperlipidemia and so on, although they could influence inflammation, were included and recorded as other medical condition.

The charts of 181 inpatients diagnosed with unipolar depressive disorder were initially assessed, and four cases were excluded based on the abovementioned criteria. Consequently, 177 patients were enrolled in the study and subsequently categorized into mild to moderate anxious distress and moderate–severe to severe anxious distress groups. In accordance with the *DSM-5* definition of depressive disorders, it is possible to refer to the current severity of symptoms using the "with anxious distress" specifier as follows: mild (two symptoms), moderate (three symptoms), moderate–severe (four or five symptoms) and severe (four or five symptoms with motor agitation). In the present study, these diagnoses were made based on HAM-D scores derived from the general chart documentation at the initial hospitalization of the patient. The HAM-D data are included in conjunction with the data from the agitation (0 = none, 1 = fidgetiness, 2 = playing with hand, hair, etc., 3 = moving about, cannot sit still, and 4 = hand-wringing, nail-biting or biting of lips) and anxiety–psychic (0 = no difficulty, 1 = subjective tension and irritability, 2 = worrying about minor matters, 3 = apprehensive attitude apparent face or speech, and 4 = fears expressed without questioning) subscales. Based on these subscales, the patients were categorized into either the mild to moderate anxious distress group (anxiety–psychic≤2 and agitation≤2, including non-anxious patients; anxiety–psychic≤1 and agitation≤1) or the moderate–severe to severe anxious distress group (anxiety–psychic≥3, regardless of agitation or agitation≥3, regardless of anxiety–psychic). The "Anxiety-Somatization" subscale of the HAM-D was not considered in the present study because the definition of the *with anxious distress* specifier in the *DSM-5* includes psychic symptoms rather than somatic symptoms (Table 1).

2.2. Assessments

All observed changes regarding the current severity of the "with anxious distress" specifier were assessed using the scores on the Agitation and Anxiety–Psychic subscales of the HAM-D that were obtained at the initial hospitalization. In addition, the charts of the patients were reviewed to evaluate primary measures, including various immune factors such as CRP levels and WBC counts (neutrophils, lymphocytes and monocytes), the presence of confounding factors such as smoking, other general medical disorders (chronic disorders, hypertension, diabetic mellitus, dyslipidemia, well-modulated thyroid disorder, surgical history, etc.) and body mass index (BMI; kg/m^2), and secondary measures including demographic and clinical characteristics such as age, sex, total HAM-D scores (total depression severity), comorbidities (personality disorder, anxiety disorder, substance use disorder etc.), suicidality (defined as any suicide attempts during the patient's lifetime, including this admission), psychotic features and prescription patterns of antidepressants (selective serotonin reuptake inhibitors [SSRIs], serotonin and norepinephrine reuptake inhibitors [SNRIs], noradrenergic and specific serotonergic antidepressants [NaSSAs] etc.), mood stabilizers (lithium, valproic acid, carbamazepine, lamotrigine etc.) and antipsychotics (aripiprazole, quetiapine, olanzapine, ziprasidone, amisulpride, blonanserin, pimozide etc.), which were derived from the discharge prescription documentation. In this hospital, CRP and WBC levels are measured within 48 h of hospitalization between 06:00 and 08:00 in the morning. CRP levels were measured using immunoturbidimetry (normal range: 0.0–5.0 mg/l), and WBC counts were measured using flow cytometry (normal range: 5000–10,000 cells/mcL; differential count: neutrophil, 55–75% relative value, lymphocyte, 20–44% relative value and monocyte, 2–8% relative value).

The index episode for each patient was defined as a unipolar depressive episode that led to a hospitalization between March 2012 and April 2015. If a patient experienced more than one hospitalization during the study period, only the data from the most recent admission were analyzed. To identify the severity of anxious distress, each patient was evaluated for these symptoms at their initial hospitalization using the HAM-D.

2.3. Statistical analysis

All statistical analyses were performed using Statistical Analysis System (SAS) for Windows, Version 9.3 (SAS Institute; Cary, NC, USA). Chi-square or Fisher's Exact Tests were used to assess categorical variables, and independent *t* tests were used to assess continuous variables. Logistic regression analyses were used to analyze categorical variables and analysis of covariance (ANCOVA) tests were used to analyze continuous variables with clinical characteristics, such as total HAM-D, included as covariates for adjustment. A $P<0.05$ was considered to indicate statistical significance while a *p*-value of 0.05–0.10 indicated a trend toward statistical significance.

2.4. Ethics

This study was conducted according to the Declaration of Helsinki and was approved by the institutional review board. The board determined that informed consent was unnecessary because this was a