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Research report

Presence of psychological distress symptoms associated with onset-related life events in patients with treatment-refractory depression

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ABSTRACT

Background: Previous studies have reported that various non-life-threatening life events could cause psychological distress symptoms like posttraumatic stress disorder in adults and adolescents. We examined whether patients with treatment-refractory depression (TRD) perceive their experiences of life events, of which they think as triggering the onset of depression, as more serious psychological distress symptoms than remitted or mildly symptomatic patients with major depressive disorder (MDD).
Methods: This study employed a cross-sectional design. We recruited 78 outpatients consisting of 31 TRD patients, 31 remitted MDD patients, and 16 mildly symptomatic MDD patients. We adopted the Impact of Event Scale-Revised (IES-R) to assess the severity of psychological distress symptoms associated with the events that patients thought as triggering the onset of depression. We also evaluated clinical features and variables including the Hamilton Depression Rating Scale (HDRS).
Results: The mean [± SD] score of the IES-R in patients with TRD (46.7 [15.1]) was significantly higher than in remitted (10.3 [9.9], $p < 0.001$) or mildly symptomatic (31.3 [7.7], $p < 0.001$) patients with MDD. The HDRS scores showed significant correlations with those of the IES-R among all patients ($r = 0.811$).
Limitations: This study was not able to exclude the possibility that the severity of psychological distress symptoms associated with onset-related events could influence the difficult therapeutic course in patients with TRD due to the cross-sectional design.
Conclusions: This study demonstrated that patients with TRD perceive their onset-related life events as serious psychological distress symptoms. This result contributes to understanding the pathophysiology of TRD.

1. Introduction

Major depressive disorder (MDD) is a common mental illness with a high social burden. Although pharmacotherapy such as antidepressants plays a pivotal role in the treatment of MDD, approximately 20–30% of antidepressant-treated patients with MDD are classified as having treatment-refractory depression (TRD) (Fava and Davidson, 1996; Keller et al., 1992). Previous studies suggest that the concept of TRD is advocated as a failure to achieve sufficient remission after at least two adequate antidepressant treatment trials during a current depressive episode (Schlaepfer et al., 2012; Schosser et al., 2012; Souery et al., 2006). Therefore, it is necessary to further investigate the clinical features of TRD, to understand the pathophysiology of TRD, and to develop better management of patients with TRD.

Accumulating evidence has reported that physical and psychological stresses are closely linked with depression (Flynn and Himle, 2011). Some reports show that various stressful life events (e.g., divorce, unemployment, and public humiliation), which by themselves do not lead to fatal outcomes, could trigger depressive disorders (Brown et al., 1995; Honkalampi et al., 2005; Hosang et al., 2010; Kendler et al., 1998; Tennant, 2001). Moreover, it was reported that stressful life events cause symptoms such as intrusion, avoidance, and hyperarousal similar to posttraumatic stress disorder (PTSD) in adults and adolescents (Meiser-Stedman et al., 2012; Mol et al., 2005). A recent study suggests that childhood trauma (e.g., emotional neglect, psychological abuse) is associated with chronic and refractory depression in adults (Hovens et al., 2012). However, it is unknown whether patients with TRD perceive psychological distress symptoms as being related to adulthood life events, of which they think as triggering the onset of depression (here called "onset-related events"). Therefore, we developed the hypothesis that patients with TRD perceive symptoms of psychological distress including intrusion, avoidance, and hyperarousal as being associated with the life events, of which they thought as triggering the onset of

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depression (here called "onset-related psychological distress symptoms") similar to patients with PTSD.

The purpose of this study was to determine whether patients with TRD perceive their experiences of onset-related events as psychological distress symptoms. We conducted a cross-sectional study to assess onset-related psychological distress symptoms in patients with TRD, and compare them with remitted MDD patients or mildly symptomatic patients with MDD. In addition, we explored the factors of onset-related psychological distress symptoms in terms of severity of depression, clinical features such as bipolarity, childhood experiences of abuse or stressful events, strength of onset-related events, and duration of illness or treatment.

2. Methods

2.1. Study design

Our study employed a cross-sectional design and was approved by the ethics committee of Chiba University Graduate School of Medicine, Sodegaura Satsukidai Hospital, and Fujita Hospital. All subjects provided written informed consent for their participation in this study after the procedure had been fully explained to them.

2.2. Participants and procedure

We surveyed potential candidates from available outpatient charts at Chiba University Hospital, Sodegaura Satsukidai Hospital, and Fujita Hospital. This study was conducted from November 2012 to November 2013. All subjects were outpatients with ages ranging from 20 to 79 years, and were diagnosed with MDD according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, text revision (DSM-IV-TR) criteria (American Psychiatric Association, 2000) using the Japanese version of the Mini International Neuropsychiatric Interview (M.I.N.I.) (Otsubo et al., 2005; Sheehan et al., 1998). We excluded patients with PTSD, schizophrenia, bipolar disorders, comorbid dementia, organic mental disorder, alcohol or drug dependence, mental retardation, or impending suicide attempt. We also excluded patients who were hospitalized, under 20 years old, showing poor compliance with medication, and uncertain about their life events related to the onset of depression. A total of 247 outpatients underwent eligibility screening for the study, 158 patients did not meet the criteria for eligibility, and 89 patients were eligible to be included in the study. Nine patients declined an interview, and 2 patients answered that they experienced no life events related to the onset of depression. Finally, 78 patients participated in this study.

2.3. Assessment of depression and definition of TRD

We assessed the severity of depression using the Structured Interview Guide for the 17-item Hamilton Depression Rating Scale (HDRS-17) (Hamilton, 1967, Williams, 1988). We applied the criteria for TRD and non-TRD (i.e., remitted or mildly symptomatic depression) using the study protocol of Schosser et al. (2012) as a reference. In this study, TRD was defined as not reaching an HDRS-17 score of 17 or fewer points after two or more antidepressant treatment trials with adequate dosage and sufficient duration (i.e., longer than four weeks in the current depressive episode). Non-TRD was defined as achieving 17 or fewer point of the HDRS-17 after a single antidepressant treatment or after a second course after initial treatment failure. Moreover, within non-TRD, remission of MDD was defined as 7 or fewer points of the HDRS-17 score (Frank et al., 1991). The patients who met neither TRD nor remitted MDD criteria with an HDRS-17 score between 8 and 17 points, were categorized as intermediate MDD.

2.4. Assessments of clinical characteristics

We assessed demographic data such as age, gender, comorbidity, physical diseases, family history of psychiatric disorders in first-degree relatives, years of education, current employment, present medication, disease and therapy duration, childhood stressful life events and abuse before reaching an age of 15 years, and clinical features of atypical depression according to the DSM-IV-TR definition. In the current study, physical diseases included patients under treatment for hypertension, diabetes, hyperlipidemia, lumber disc hernia, and ulcerative colitis. Childhood life events and abuse consisted of any of the following: the experience of parental divorce, bereavement after the loss of a parent, the experience of strong violence or violent language from parent or other people, sexual harassment or abuse, neglect, the intervention by the child consultation center, or other stressful experiences.

2.5. Measures

2.5.1. The Impact of Event Scale-Revised

The Impact of Event Scale-Revised (IES-R) is a self-report measure for assessing the severity of symptomatic responses to stressful life events in the past seven days and consists of 22 items and three subcategories, including intrusion (8 items: intrusive thoughts, nightmares, intrusive feelings and imagery, re-experiencing), avoidance (8 items: numbing of responsiveness and avoidance of feelings, situations, and ideas), and hyperarousal (6 items: sleep difficulties, anger outbursts, irritability, hyper-vigilance, difficulty concentrating, and increased startle) (Weiss and Marmar, 1997). Each item is rated on a 5-point scale (0=not at all, 1=a little, 2=moderately, 3=a lot, 4=enormously). The total sum of points ranges from 0 to 88. The internal consistency and concurrent validity of the IES-R were confirmed (Baumert et al., 2004). The Japanese version of the IES-R has already been standardized (Asukai et al., 2002). The IES-R was developed and has been widely used to evaluate traumatic symptoms in patients with PTSD (Weiss and Marmar, 1997), and covers all aspects of PTSD symptoms such as intrusion, avoidance, and hyperarousal. Because we hypothesized that patients with TRD could perceive onset-related psychological distress symptoms similar to patients with PTSD, as described in the introduction, we adopted the IES-R to evaluate onset-related psychological distress symptoms in this study. We instructed patients to write their onset-related event into the blank space of the introduction document of the IES-R, and to answer each item of the IES-R regarding their onset-related event.

2.5.2. Life Change Units Value

To evaluate stress level of life events objectively, we used the social readjustment rating scale and scored by the means of Life Change Units Value (LCU) (Holmes and Rahe, 1967). The LCU is a rating scale to measure the stress of life events proposed by Holmes and Rahe and is based on their multifaceted and extensive investigation. The stress of important life events is quantified from 11 to 100 points. For example, 100 points for the spouse's death, 73 for divorce, 53 for one's disease or impairment, 50 for marriage, and 20 for change of address.

2.5.3. Assessment of bipolarity

We further defined the patients as having bipolarity if they satisfied the criteria of either "bipolar spectrum disorder" (Ghaemi et al., 2002) or "bipolarity specifier" (Angst et al., 2003a, 2003b). We examined bipolarity in all participants, because several studies have demonstrated that there could be a high prevalence of bipolarity in patients with TRD (Correa et al., 2010; Dudek et al., 2010; Parker et al., 2005). The concept of bipolar spectrum and bipolarity specifier, which suggests that depressive patients with