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

（難治性うつ病患者における、ライフイベントへのトラウマ様症状の存在）

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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.

Key words: treatment-refractory depression, life events, psychological distress

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 stress 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 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 sub-categories, 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, 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 was 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, 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 subthreshold hypomanic episodes or characteristics of bipolar disorder should be considered closer to bipolar depression rather than unipolar depression, has been of importance in terms of assessing the clinical condition of mood disorders (Angst and Marneros, 2001).

2.5.4 Assessment of patient's impression for onset-related events

We also examined the perceived causal relationship between incidence of depression and onset-related event among the patients, using our original questionnaire form, which asked each participant to simply answer how much they rated the causal relationship between incidence of depression and onset-related event from 1 to 100 percent.

2.6 Primary Endpoint

The score of the IES-R for onset-related events for the three groups was set as the primary endpoint in this study.

2.7 Statistical Analysis

We analyzed the data separately for the three groups including TRD, intermediate,

and remission group. We performed all analyses using SPSS for Windows, Version 19. We employed Chi-square or Fisher's exact test for categorical variables and Student's t-test or one-way ANOVA for the other variables. We performed one-way ANOVA for total and sub-category scores of the IES-R and HDRS-17, followed by Games-Howell test for multiple comparisons. We also tested the correlation between HDRS and IES-R by means of Pearson's product moment correlation. The level of significance was set at $p < 0.05$ and the level for power at 0.80.

3. Results

3.1 Characteristics

Table 1

Characteristics of the patient group with treatment-refractory depression (TRD), intermediate group, and remission group.

	TRD (n = 31)	Intermediate (n = 16)	Remission (n = 31)	p value
Age, years (SD) [Age range]	47.3 (12.6) [24–64]	48.6 (12.7) [28–67]	53.5 (13.8) [25–77]	NS
Gender, male/female	13/18	5/11	12/19	NS
Education, years (SD)	13.2 (2.5)	13.0 (2.4)	13.9 (1.8)	NS
Current employment (%)	10 (32.3)	9 (56.3)	15 (48.4)	NS
Psychiatric comorbidity (%)	8 (25.8)	4 (25.0)	4 (12.9)	NS
Physical disease (%)	19 (61.3)	8 (50.0)	20 (64.5)	NS
Family psychiatric history (%)	13 (41.9)	7 (43.8)	8 (25.8)	NS
Childhood life events and abuse (%)	10 (32.3)	7 (43.8)	7 (22.6)	NS
LCU of life events, points (SD)	48.1 (30.0)	50.4 (22.8)	44.2 (24.7)	NS
HDRS-17 items, points (SD)	23.2 (3.4)	11.5 (3.0)	3.6 (2.0)	$< 0.001^{*}$
Atypical depression (%)	5 (16.1)	1 (6.3)	1 (3.2)	NS
Disease duration, months	87.5 (52.6)	85.4 (70.6)	94.3 (69.9)	NS
Therapy duration, months	70.8 (41.9)	73.9 (61.2)	77.1 (71.7)	NS

Note: Variables represent mean (standard deviation: SD)

Abbreviations: LCU, Life Change Units Value; HDRS, Hamilton Depression Rating Scale; NS, not significant.

*The data for three groups were analyzed with one-way ANOVA, followed by Games-Howell test for multiple comparisons.

The characteristics of participants included in the analysis are presented in Table 1.

The 78 patients with MDD consisted of three groups: the TRD group (n = 31),

remission group (n = 31), and intermediate group (n = 16). There were no significant differences in age, gender, and years of education between the three groups. Furthermore, there were no significant differences in the proportion of current employment, physical diseases, psychiatric comorbidity, and first-degree relatives with psychiatric disorders between the three groups. As for the breakdown of psychiatric comorbidities, there were patients with dysthymic disorder (n = 3), social anxiety disorder (n = 3), panic disorder (n = 1), generalized anxiety disorder (n = 1), pain disorder (n = 1), and bulimia nervosa (n = 1) in the TRD group, and two patients of this group suffered from double psychiatric comorbidities. Psychiatric comorbidities in the intermediate group consisted of social anxiety disorder (n = 1), panic disorder (n = 2), generalized anxiety disorder (n = 1), and obsessive-compulsive disorder (n = 1), and one patient of this group suffered from double comorbidity. In the remission group, psychiatric comorbidities included social anxiety disorder (n = 1), panic disorder (n = 1), generalized anxiety disorder (n = 1), and obsessive-compulsive disorder (n = 2), and one patient suffered from double comorbidity.

Table 2

The breakdown of onset-related life events and the patient's impression about causal relationship between incidence of depression and onset-related event.

	TRD (n = 31)	Intermediate (n = 16)	Remission (n = 31)
Job-related events	15	4	20
Family-related events	14	6	6
Health-related events	5	2	7
Money-related events	3	1	1
Other events	1	3	0
Overlapping events	7	0	1
Patients' impression of causal relationship between their events and depression*	n	n	n
100 %	10	3	9
81–99 %	12	7	14
61–80 %	6	2	4
41–60 %	2	3	4
21–40 %	1	1	0
1–20 %	0	0	0

Abbreviation: TRD, treatment-refractory depression

*Degree in percentage of patients' impression of causal relationship between their stressful life events around the time of onset and depression.

Table 2 shows the breakdown of onset-related life events among all participants. Many patients thought there was greater than 80% in percentage of patients' impression of causal relationship between their stressful life events around the time of onset and depression (70.9% in TRD, 62.5% in intermediate, and 74.2% in remission group).

Table 3

Medication profiles of the three patient groups.

Class of medication	TRD (n = 31) n	Intermediate (n = 16) n	Remission (n = 31) n
Antidepressants (AD)			
SSRI	17	7	16
SNRI	8	5	4
NaSSA	4	3	5
Trazodone	2	2	2
Other	4	3	6
Total	35	20	33
Benzodiazepine (BZ)	22	9	19
Mood stabilizers (MS)			
Lithium	2	0	1
Valproic acid	2	1	0
Lamotrigine	5	0	0
Total (MS)	9	1	1
Antipsychotics (AP)			
Olanzapine	1	2	0
Quetiapine	3	0	0
Aripiprazole	1	0	1
Other	1	0	0
Total (AP)	6	2	1
Medication combination			
Single drug (AD)	1	4	9
Two AD	1	1	0
AD+BZ	12	7	16
AD+MS	3	0	1
AD+AP	1	0	1
Three or more classes	8	2	0
Other	5	2	4

Abbreviation: TRD, treatment-refractory depression

Table 3 shows the medication profiles for all participants. The combination of

antidepressant and benzodiazepine was the predominant profile for each group (38.7% in TRD, 43.8% in intermediate, and 51.6% in remission group). The proportion of patients treated with a single antidepressant was highest in the remission group (29.0%). On the other hand, almost all patients with TRD had been treated with multiple-drug combination therapy.

3.2 The scores of the IES-R for onset-related events

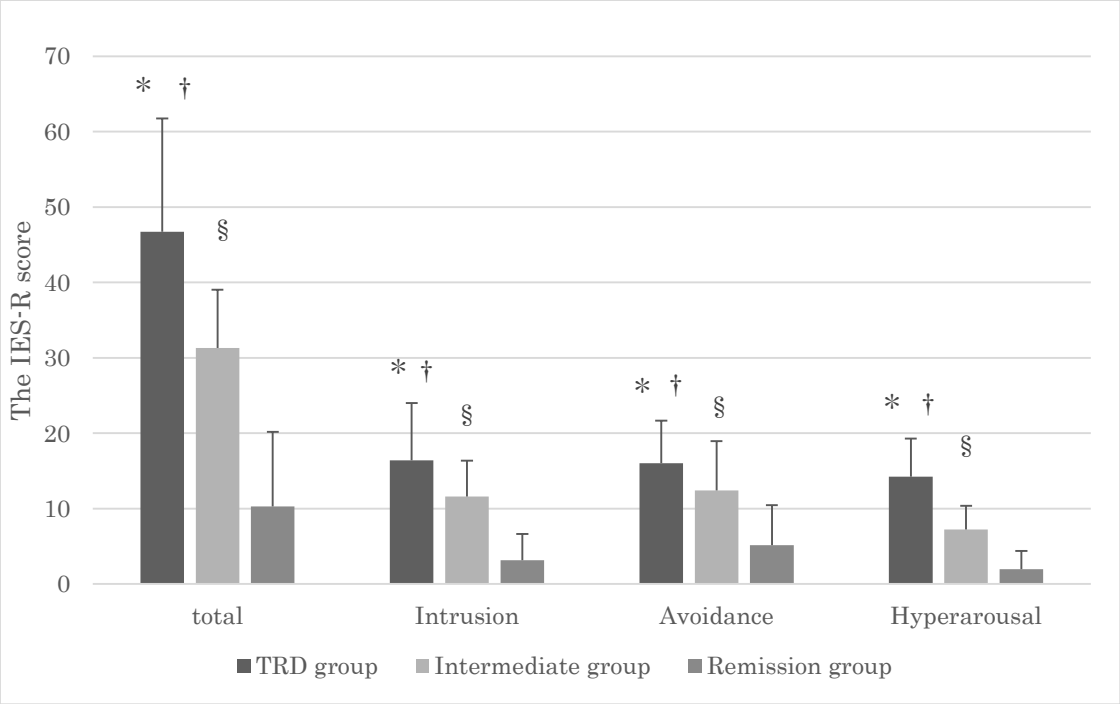

Figure 1. IES-R scores (total and sub-categories: intrusion, avoidance, and hyperarousal) for treatment-refractory depression (TRD), remission, and intermediate group.

＊Comparison between TRD and remission group ($p < 0.001$); †comparison between TRD and intermediate group ($p < 0.001$); §comparison between intermediate and remission group ($p < 0.001$).

Figure 1 shows the IES-R for onset-related events for all groups. The total score of the IES-R showed a significant difference between the three groups ($F(2) = 72.81$, $p < 0.001$). Post-hoc analysis showed significant differences between each group; the IES-R total score was significantly higher in the TRD group (mean = 46.7, standard deviation (SD) = 15.1) than intermediate (mean = 31.3, SD = 7.7; $t(45) = 4.63$, 95%CI 7.34–23.45, $p < 0.001$), and remission MDD group (mean = 10.3, SD = 9.9; $t(60) = 11.25$, 95%CI 28.61–44.23, $p < 0.001$). The total score of the IES-R was also significantly higher in the intermediate than remission group ($t(45) = 7.40$, 95%CI 14.62–27.42, $p < 0.001$).

As shown in Figure 1, for each sub-category of the IES-R, there were significant differences between the three groups: intrusion ($F(2) = 42.65$, $p < 0.001$), avoidance ($F(2) = 28.92$, $p < 0.001$), and hyperarousal ($F(2) = 81.48$, $p < 0.001$). Each sub-category score of the TRD group was significantly higher compared to the intermediate and remission group. For intrusion, the mean score of the TRD group was 16.4 (SD = 7.6), while it was lower for the intermediate (mean = 11.6, SD = 4.8) and remission group (mean = 3.2, SD = 3.5). For avoidance, the mean score of the TRD group was 16.0 (SD = 5.6), while it was lower for the intermediate (mean = 12.4, SD = 6.5) and remission group (mean = 5.2, SD = 5.3). For hyperarousal, the mean score of the TRD group was

14.3 (SD = 5.0), while it was lower for the intermediate (mean = 7.3, SD = 3.1) and remission group (mean = 2.0, SD = 2.4).

3.3 The relationship between the IES-R and the HDRS

There was a significant positive correlation between the score of the IES-R for onset-related events and the HDRS for all three groups combined ($r = 0.82$, $p < 0.001$), although there were no correlations between the two measures within each group. There were no significant correlations between the IES-R score and the duration of disease, nor were there significant correlations between the IES-R score and duration of treatment. Furthermore, there was no correlation between the IES-R score and the LCU. There were no significant differences between the scores of the IES-R for patients with or without childhood life events or abuse, neither in all patients nor in the patients with TRD.

3.4 Relationship between TRD and bipolarity

Table 4

IES-R and HDRS scores in MDD patients with or without bipolarity.

All patients	With bipolarity	Without bipolarity	T ratio[1] [d.f.]	95%CI[1]	p value[1]
78	19	59			
IES-R	41.9 (18.3)	24.9 (19.1)	3.41 [76]	7.09–26.94	0.001
HDRS	17.4 (9.1)	11.6 (9.0)	2.44 [76]	1.07–10.51	0.017

Note: Variables represent mean (standard deviation: SD)

Abbreviations: IES-R, Impact of Event Scale-Revised; HDRS, Hamilton Depression Rating Scale; MDD, major depressive disorder

[1]Statistical analysis was performed by Student's t-test.

The number of patients with bipolarity were calculated for the TRD (n = 10), intermediate (n = 6), and remission group (n = 3). The TRD group had a significantly higher ratio of patients with bipolarity than the remission group, as confirmed by a Chi-square test (p = 0.028). In more detail, the number of patients meeting the criteria of bipolar spectrum disorder were counted for the TRD (n = 2), intermediate (n = 3), and remission group (n = 0). The numbers of patients meeting the criteria of bipolarity specifier were assessed for the TRD (n = 9), intermediate (n = 5), and remission group (n = 3). One patient in the TRD and two patients in the intermediate group met the criteria of both bipolar spectrum disorder and bipolarity specifier. Table 4 shows the relationship between patients with or without bipolarity and two clinical variables such as the IES-R for onset-related events and the HDRS for all participants. The IES-R and

HDRS scores were significantly higher in patients with bipolarity than in those without bipolarity.

4. Discussion

In this study, we made three important clinical observations. First, the main finding of our study was that patients with TRD perceive their onset-related events as more serious psychological distress symptoms than patients with remitted MDD or MDD patients with mild residual depressive symptoms. Second, our results demonstrate that the severity of depressive symptoms shows a significant positive correlation with the severity of onset-related psychological distress symptoms in patients with MDD. Third, our study further shows that the clinical feature of bipolarity might be associated with severe depressive symptoms and onset-related psychological distress symptoms in patients with MDD.

The first main finding of our study was that patients with TRD think of their onset-related events as more serious psychological distress symptoms than those with remitted MDD or MDD patients with mild residual depressive symptoms. To our knowledge, this is the first study to demonstrate that patients with TRD perceive their experiences of onset-related events as serious psychological distress symptoms such as intrusion, avoidance, and hyperarousal. It has been reported that clinical factors

including comorbid psychiatric disorders such as panic disorder and anxiety disorders, current suicidal risk, lack of full remission after a previous episode, age at onset younger than eighteen years, and bipolarity are related to TRD (Dudek et al., 2010; Souery et al., 2007). Regarding additional clinical factors, it is suggested that neuroticism and excessive pessimistic and negative thinking are involved in treatment resistant depression (Thase et al., 2001). Our findings may present not only a new perspective on clinical symptoms of TRD, but also suggest additional clinical factors associated with TRD.

Our results demonstrate that the severity of depressive symptoms is positively correlated with the severity of onset-related psychological distress symptoms in patients with MDD. This result should be interpreted in two ways: (1) Onset-related psychological distress symptoms directly affect depressive symptoms and may contribute to a worse prognosis for patients with MDD, although prospective cohort studies are needed to establish this concept. (2) The severity of the depressive state may affect cognitive distortions in depressed patients, and consequently elicit onset-related psychological distress symptoms. The possibility of a cognitive negative bias induced by the depressive state should be considered further (Beck, 2008). Patients with MDD tend to have pessimistic thoughts and recognize their future as hopeless when suffering

from severe depression (Abramson et al., 1978). Consequently, it has been implied that cognitive distortions occur in depressed patients (Beck, 2008). From a neuroscience perspective, it was suggested that the human condition of depression could damage glial and neuronal cells in the hippocampus and reduce hippocampal volume (Campbell et al., 2004; Videbech and Ravnkilde, 2004). It was further reported that the morphologic change of the hippocampus could induce memory impairments in patients with depression (Sheline et al., 1999). Moreover, it was reported that the clinical condition of depression in particular induces impairment in declarative memory (Burt et al., 1995). It may be possible that patients with depression recall their past life events such as onset-related events with a bias due to distorted cognition. As a consequence of distorted cognition and memory impairment, patients with TRD may develop a more negative impression of their life events compared to mild or remitted MDD patients.

The present results showed that onset-related psychological distress symptoms are more severe in MDD patients with bipolarity than in those without bipolarity. In addition, our results suggest that TRD patients with bipolarity tend to experience severer onset-related psychological distress symptoms than TRD patients without bipolarity. It has been suggested that patients with clinical features of bipolarity share clinical similarities to patients with bipolar disorders rather than with unipolar

depression on the basis of the concept of bipolar spectrum (Akiskal, 1995; Akiskal et al., 2006). Several studies suggest that patients with bipolar disorders have a higher prevalence of PTSD than those with MDD (Otto et al., 2004; Pollack et al., 2006). A high prevalence of traumatic experiences in patients with severe mental disorder such as bipolar disorder has been reported (Mueser et al., 1998). Moreover, the relationship between bipolar disorder and PTSD has received further support by findings of molecular biology, which implicates that low secretion of brain-derived neurotrophic factor (BDNF) in the human brain may be a risk factor for the onset of PTSD (Rakofsky et al., 2012), and the production of BDNF may also be reduced in patients with bipolar disorder (Rakofsky et al., 2012). The relationship between the clinical factor of bipolarity and onset-related psychological distress symptoms in depressed patients observed in the current study might contribute to adding a new perspective to the concept of mood disorders.

Our main finding that patients with TRD perceive their onset-related events as serious psychological distress symptoms such as intrusion, avoidance, and hyperarousal could not only be useful to improve understanding of clinical features of TRD, but also presents the potential for new perspectives in the treatment of TRD. Regarding the role of psychotherapy in the management of TRD, cognitive-behavioral therapy and

interpersonal psychotherapy have been recommended as evidence-based treatments in combination with antidepressant medication (Flynn and Himle, 2011; Thase, 2013). On the basis of our finding, it may be effective to incorporate psychological intervention targeting psychological distress symptoms associated with onset-related events for patients with TRD. For example, psychotherapy techniques of prolonged exposure and cognitive restructuring may be effective in the treatment of TRD as well as PTSD (Marks et al., 1998). It was reported that prolonged exposure therapy improved symptoms of depression in patients with PTSD (Eftekhari et al., 2013). Using imaginal exposure for traumatic life-event memories or reappraising TRD patients' beliefs about their life events, which they thought as triggering the onset of depression, may be useful for the treatment of TRD.

In terms of pharmacotherapy for psychological distress, several case series reported that treatment with ifenprodil was effective for patients with PTSD, especially for treating flashbacks (Kishimoto et al., 2012; Sasaki et al., 2013). Ifenprodil is a neuroprotective drug that acts as an antagonist of the N-methyl-D-aspartate (NMDA) receptor, by binding to the GluN2B subunit (Williams, 2001). Ifenprodil also binds to the endoplasmic reticulum protein sigma-1 receptors (Hashimoto and London, 1993, 1995). Sigma-1 receptors play a role in the pathophysiology of neuropsychiatric

diseases (Hashimoto and Ishiwata, 2006). Future studies examining treatment of TRD patients by psychotherapy and pharmacotherapy, such as ifenprodil treatment, may be needed.

4.1 Limitations

Three issues need to be discussed for the limitations. First, this study was not able to exclude the possibility that the severity of onset-related psychological distress symptoms could cause the difficult therapeutic course in patients with TRD, because a cross-sectional design was implemented as the method of this study. To resolve this problem, prospective cohort studies are needed in the future. For the same reason, this study was not able to eliminate potential confounding factors, even if certain patient characteristics did not differ significantly between the three groups. Second, the limitation of the assessment method for onset-related psychological distress symptoms in patients with MDD should be acknowledged. Although the contents of the IES-R cover all aspects of psychological traumatic symptoms, the IES-R has been originally developed and used for a rating scale of PTSD severity. To establish validity and reliability of the assessment of onset-related psychological distress symptoms, further studies are needed to include a multilateral approach to assess symptoms of

psychological distress in patients with MDD. Third, the recall bias might present an additional problem with this study, because the participants were requested to recall past life events.

5. Conclusion

This study confirmed that patients with TRD perceive their experiences of onset-related events as serious psychological distress symptoms. Future studies should be conducted to confirm distress symptoms in MDD or depressed patients with a wide range of clinical features, and to investigate the pathophysiology of psychological distress in patients with TRD through neuropsychological examinations and brain imaging techniques.

Contributors

Study concept and design: Kimura, Hashimoto, Iyo
Acquisition of data: Kimura, Hashimoto
Analysis and interpretation of data: Kimura, Hashimoto, Niitsu, Iyo
Statistical analysis: Kimura, Hashimoto, Niitsu
Drafting of the manuscript: Kimura, Hashimoto
Critical revision of the manuscript for important intellectual content: Kimura, Hashimoto, Niitsu, Iyo
Study supervision: Iyo

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Conflict of interest

We declare no conflicts of interest.

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