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Research paper

Circadian rhythm sleep-wake disorders as predictors for bipolar disorder in patients with remitted mood disorders

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ABSTRACT

Background: Circadian rhythm dysfunction is thought to play a key role in the pathogenesis of bipolar disorder (BD). We focused on circadian rhythm sleep-wake disorders (CRSWD) as possible predictors for bipolar disorder in patients with remitted mood disorders.

Method: One hundred four BD (41 type I and 63 type II) outpatients and 73 age- and sex-matched major depressive disorder (MDD) outpatients participated in this study. The subjects were asked to answer questionnaires including demographic variables, clinical course of the disorder, and family history of psychiatric disorders. Severity of mood status was evaluated by the Montgomery-Åsberg Depression Rating Scale and Young Mania Rating Scale. CRSWD was diagnosed by clinical interview and sleep logs based on the International Classification of Sleep Disorders, third edition.

Results: The rate of CRSWD in BD subjects was significantly higher than that in MDD subjects (33.7% vs 9.6%; $P < 0.001$). A multiple logistic regression analysis revealed that comorbid CRSWD (OR = 3.35, 95% CI = 1.24 – 9.07; $P = 0.018$), two or more previous mood episodes within the past year (OR = 3.57, 95% CI = 1.10 – 11.63; $P = 0.035$), and antidepressant-related switch to mania/hypomania (OR = 10.01, 95% CI = 1.20 – 83.52; $P = 0.033$) were significantly associated with BD in patients with remitted mood disorders.

Conclusion: CRSWD, as well as other factors, could be diagnostic predictors for BD in patients with remitted mood disorders. Combinations of these factors might be useful for predicting a BD diagnosis among the mood disorders in a clinical setting.

1. Introduction

Bipolar disorder (BD) is a chronic disorder with repeated relapse and recurrence through its clinical course. For preventing these, appropriate diagnosis and treatment of the disorder is desirable. On the other hand, it is difficult for clinicians to distinguish BD from major depressive disorder (MDD), particularly in the early stage of the disorders mainly because depressive symptoms are common in both BD and MDD. In addition, two-thirds of BD patients develop the disorder initially with a depressive episode (Daban et al., 2006) and depressive episodes are more frequent than manic/hypomanic episodes in the clinical course of BD (Solomon et al., 2006). As a result, an appropriate diagnosis of BD is most likely to be made long after the onset of the disorder in clinical settings (Akiskal et al., 1995). Consequently, BD patients who are misdiagnosed with MDD receive inappropriate treatment with antidepressants, which may cause antidepressant-related manic/hypomanic episodes and rapid cycling (Kanba et al., 2013) and increase the risk of suicidal attempts (Altamura et al., 2010). Therefore, clinicians should provide appropriate diagnosis and treatment for BD patients as soon as possible after the onset of the disorder.

Previous studies have suggested some clinical predictors for differentiating BD from MDD (Angst et al., 2011; Inoue et al., 2015; Perlis et al., 2006; Takeshima and Oka, 2013; Xiang et al., 2013). Family history of bipolar disorder (Angst et al., 2011; Perlis et al., 2006; Takeshima and Oka, 2013), younger onset age of mood disorders (Angst et al., 2011; Inoue et al., 2015; Perlis et al., 2006; Takeshima and Oka, 2013; Xiang et al., 2013), and larger number of mood episodes (Angst et al., 2011; Inoue et al., 2015; Perlis et al., 2006; Takeshima and Oka, 2013; Xiang et al., 2013) have been identified as predictors for BD in several studies. Moreover, some studies identified other predictors for the diagnosis of BD among the mood disorders, such as the presence of mixed depression (Angst et al., 2011; Inoue et al., 2015; Takeshima and

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Oka, 2013), positive history of suicidal attempts (Inoue et al., 2015), cyclothymic temperament (Takeshima and Oka, 2013), and antidepressant-related mania/hypomania (Angst et al., 2011; Inoue et al., 2015). Nevertheless, it is still not easy for clinicians to diagnose BD in the early stage of the disorder because the above predictors are difficult to identify soon after the onset of the disorder. Therefore, we should identify the factors observed, even in the early stage of BD, which might be correlated with the pathogenesis of BD.

Recently, several studies have suggested that circadian rhythm dysfunction plays a crucial role in the pathogenesis of BD (Abreu and Braganca, 2015; Harvey, 2008; Murray and Harvey, 2010). Decreased needs for sleep in a manic episode and hypersomnic or insomnolent symptoms in a depressive episode are included in the diagnostic criteria of BD in the Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-5) (American Psychiatric Association, 2013). Even in euthymic periods, instabilities of sleep-wake cycles in BD patients have been frequently observed (Jones et al., 2005; Ng et al., 2015; Salvatore et al., 2008), possibly suggesting that the existence of circadian rhythm dysfunction might be a biological marker for BD. Our previous study also suggested a clearly high prevalence of circadian rhythm sleep-wake disorders (CRSWD) in euthymic BD patients and the possible relationship between circadian rhythm dysfunction and the pathophysiology of BD (Takaesu et al., 2016). Of note, a recent study reported that circadian rhythm dysfunction in BD patients was more severe than that in MDD patients (Duarte Faria et al., 2015). Taking these together, circadian rhythm dysfunction could be a possible predictor for BD in patients with mood disorders.

However, apparently no study has focused on circadian rhythm dysfunction as a possible predictor for BD in patients with mood disorders. Therefore, the aim of this study was to test the hypothesis that circadian rhythm dysfunction could be a predictor for the diagnosis of BD in patients with remitted mood disorders.

2. Methods

This study was approved by the ethics committee of Tokyo Medical University and conducted after obtaining written informed consent from the subject patients. Patients with BD and MDD were diagnosed by fully trained attending psychiatrists according to the Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-5) (American Psychiatric Association, 2013). All patients had been seen by fully trained attending psychiatrists in our outpatient clinic for years. The clinical course, episodes, and other clinical information were recorded on electronic medical charts using routine clinical interviews and observations and were diagnosed by fully trained attending psychiatrists. We included BD patients who visited the outpatient clinic of the Psychiatry Department at Tokyo Medical University Hospital from August 2014 to January 2015. Participants were included if they were in remission as defined by the Young Mania Rating Scale (YMRS < 7 points) and Montgomery-Åsberg Depression Rating Scale (MADRS < 13 points) for at least 8 weeks prior to the investigation (Steinan et al., 2014). Exclusion criteria were as follows: (1) comorbid with severe physical disease, (2) comorbid with organic brain diseases, (3) alcohol or substance abuse, (4) shift worker, (5) having suicidal ideation, (6) history of admission to the hospital within the previous 8 weeks, or (7) having visual impairments, an important cause of CRSWD (Sack et al., 1992). As a result, we included 104 remitted BD patients from 127 consecutive BD patients, who were almost the same as BD subjects in our previous study except for 3 cases (Takaesu et al., 2016). We selected 104 MDD patients by matching age and sex with BD patients based on a table of random numbers from 304 consecutive MDD patients in our outpatient clinic from March 2015 to August 2015. Subsequently, we recruited MDD patients with the same inclusion and exclusion criteria as the ones for the BD participants, except for YMRS cutoff scores. Finally, 73 MDD patients met the criteria for this study, which is the sample size to enable the multivariate logistic regression analysis including six independent variables. This study was part of a larger study conducted between August 2014 and January 2016, another part of which was already published (Takaesu et al., 2016).

All subjects were asked to answer questionnaires including demographic information, clinical course of the mood disorders, clinical predictors for BD already identified in previous studies (Inoue et al., 2015) (earlier onset age [< 25 years], two or more previous mood episodes within the past year, family history of bipolar disorder in first-degree relatives, antidepressant-related switch to mania/hypomania, and history of suicide attempt). The definition of antidepressant-related switch to mania/hypomania was based on the diagnostic criteria of substance/medication-induced bipolar and related disorders of DSM-5 (American Psychiatric Association, 2013), which may include subthreshold symptoms of mania or hypomania that do not persist beyond the physiological effects of antidepressants, if the causal relationship is clear. CRSWD was diagnosed by a board-certified sleep specialist physician (Y. T.) by using the criteria of the International Classification of Sleep Disorders, third edition (ICSD-3) (American Academy of Sleep Medicine, 2014) based on thorough clinical interviews and sleep logs recorded by patients themselves for more than 4 weeks.

The Mann-Whitney *U*-test was used for the comparison of continuous variables and MADRS and YMRS scores between the BD and MDD groups. The chi-square test or Fisher's exact test for two groups was used for the comparison of categorical variables. The Kruskal-Wallis test, followed by the Bonferroni test, was performed to compare the rates of CRSWD comorbidity among the BD I, BD II, and MDD groups.

To identify significantly associated factors for the diagnosis of BD in the subject patients with remitted mood disorder, a series of logistic regression analyses was performed with 6 independent variables (aforementioned ones including earlier onset age [< 25 years], two or more previous mood episodes within the past year, family history of bipolar disorder in their first-degree relatives, antidepressant-related switch to mania/hypomania, history of suicidal attempt, and comorbid CRSWD). All variables were initially examined by univariate analyses. To control for confounding factors and to determine the main correlates, we performed multivariate logistic regression analyses for all variables.

SPSS version 24 software for Windows (SPSS Inc., Chicago) was used for all the statistical analyses. A P value of less than 0.05 was considered to indicate a statistically significant difference.

3. Results

The prevalence of CRSWD in the BD group was significantly higher than that in the MDD group (BD, n = 35, 33.7% vs MDD, n = 7, 9.6%; $P < 0.001$). There was a significant difference in the rates of CRSWD comorbidity among the three groups (BD I, 34.1%; BD II, 33.3%; MDD, 9.6%; $P = 0.001$). Post-hoc analyses showed that the rates of CRSWD comorbidity in the BD I ($P = 0.010$) and BD II ($P = 0.004$) groups were significantly higher than that in the MDD group. However, there was no significant difference in the rates of CRSWD comorbidity between the BD I and BD II groups ($P = 1.000$). As for the sub-categories of CRSWD according to the ISCD-3 criteria, 27 subjects in the BD group and 7 subjects in the MDD group met the criteria for delayed sleep-wake phase disorder, which is characterized by a delayed phase of major sleep episode (Ahmed and Thorpy, 2007; Auger et al., 2015) (Takaesu et al., 2016) (Table 1). Six subjects in the BD group and one subject in the MDD group met the criteria of non-24-h sleep-wake rhythm disorder, which is characterized by non-entrainment of circadian rhythm to a 24-h light/dark cycle (Ahmed and Thorpy, 2007; Auger et al., 2015) (Table 1). Two subjects in the BD group met the criteria for irregular sleep-wake rhythm disorder, which is characterized by a lack of a clearly defined sleep-wake phase (Ahmed and Thorpy, 2007; Auger et al., 2015) (Table 1). Fig. 1 shows characteristic examples of sleep logs in subcategories of CRSWD in the BD and MDD subjects.