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Research report

Psychomotor agitation in major depressive disorder is a predictive factor of mood-switching

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ABSTRACT

Background: The relationship between psychomotor agitation in unipolar depression and mood-switching from depression to manic, hypomanic and mixed states has been controversial. We investigated the future risk of initial mood-switching as a function of psychomotor agitation in unipolar depression.

Methods: We identified 189 participants diagnosed with major depressive disorder (MDD). We divided all patients with MDD into two categories (1) agitated patients ($n=74$), and (2) non-agitated patients ($n=115$). These groups were prospectively followed and compared by time to mood-switching. Kaplan–Meier survival curves, log-rank test for trend for survivor functions, and Cox proportional hazard ratio estimates for a multivariate model were conducted to examine the risk of mood-switching by psychomotor agitation.

Results: During follow-up, mood-switching occurred in 20.3% of the agitated patients and 7.0% of the non-agitated patients. In the Kaplan–Meier survival estimates for time to incidence of mood-switching with agitated or non-agitated patients, the cumulative probability of developing mood-switching for agitated patients was higher than those for non-agitated patients (log-rank test: $\chi^2=7.148$, df=1, $p=0.008$). Survival analysis was also performed using Cox proportional hazards regression within a multivariate model. The agitation remained significantly associated with incidence of mood-switching (HR=2.98, 95% CI: 1.18–7.51).

Limitations: We did not make a clear distinction between antidepressant-induced mood-switching and spontaneous switching.

Conclusions: The main finding demonstrated that MDD patients with agitation were nearly threefold as likely to experience mood-switching, suggesting that psychomotor agitation in MDD may be related to an indicator of bipolarity.

1. Introduction

Most cases of bipolar disorder (BPD) are diagnosed as major depressive disorder (MDD) before the appearance of any manic episode. Many such depressed patients are at risk for mood-switching from depression to manic, hypomanic and mixed states, sometimes in association with antidepressant treatment. Current systematic review indicated that mood-switching occurred in 8.18% of medicated patients with unipolar MDD (Baldessarini et al., 2013). Such risk may be particularly high among patients with clinical features of psychosis or retardation, history of depressive recurrences, family history of mood disorders, antidepressant treatment and earlier onset-age (Akiskal et al., 1983; Angst et al., 2005; Goldberg et al., 2001; Tondo et al., 2013). Although these risk elements have purportedly been related to "bipolarity", the definition of bipolarity may not be firmly established.

Psychomotor agitation is a component of diagnostic criteria for both major depressive episodes and excited polarity episodes on the Diagnostic and Statistical Manual for Mental Disorders, 4th edition (DSM-IV) (American Psychiatric Association, 2000). The diagnostic validity and utility of agitated depression in the classification of mood disorder are unclear. Historically, Kraepelin (1904) interpreted agitated depression only partially as a mixed state of circular depression within

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"manic-depressive insanity". Abrams and Taylor (1974) suggested a higher frequency of psychomotor agitation in depressive episodes of BPD. Spitzer et al. (1978) described that agitated depression is a subtype of MDD using the Research Diagnostic Criteria (RDC). Recently, Maj et al. (2003) reported that psychomotor agitation was found more frequently in depressive episodes of BPD. Moreover, Akiskal et al. (2005) indicated that even agitated depression in patients strictly diagnosed with unipolar MDD has bipolar features, and suggested that agitated unipolar depression should be classified as a depressive mixed state belonging to the broader bipolar spectrum. On the other hand, another report indicated that psychomotor agitation was more common in unipolar depression (Katz et al., 1982). Angst et al. (2009) indicated in their Zurich Study that psychomotor agitation was more frequently found in unipolar depression than in bipolar individuals, and their findings failed to support the hypothesis that psychomotor agitation in depression indicated the presence of bipolarity.

In the case of individuals with bipolar depression medicating with antidepressants, the International Society for BPD recommends that such patients should be closely monitored for signs of increased psychomotor agitation to prevent mood-switching (Pacchiarotti et al., 2013). However, when patients with unipolar depression present a symptom of psychomotor agitation, it is unclear whether the symptom may predict mood-switching. To our knowledge, little is known about the relationship between psychomotor agitation in unipolar depression and mood-switching from depression to manic, hypomanic and mixed states.

The aim of the present study was to clarify whether psychomotor agitation is more associated with indicators of bipolarity. Thus, we investigated the future risk of mood-switching in unipolar depression with and without psychomotor agitation. The present study is a part of the Juntendo University Mood Disorder Project (JUMP).

2. Methods

2.1. Subjects

A total of 206 JUMP study participants with MDD (79 males and 127 females; mean age, 55.8 years; age range, 21–85 years) were recruited from the Juntendo Koshigaya Hospital, in Saitama, Japan, between April 2004 and March 2013. Diagnoses were made according to DSM-IV criteria. Depressive symptoms were assessed using the Hamilton Rating Scale for Depression (HAM-D) (Hamilton, 1960) at the time of hospital admission. We divided all patients with MDD into agitated patients (defined as a score ≥ 1 on the HAM-D subscale item of "Agitation", $n=81$) and non-agitated patients (a score$=0$ on item of "Agitation" on HAM-D, $n=125$). Patients were excluded if they had a comorbid axis-I disorder, a history of other psychiatric disorders, severe or acute medical illnesses, neurological disorders, or used any drugs that may trigger depression. Furthermore, at recruitment, patients with depressive mixed states were excluded using criteria of DSM-IV.

All patients were on antidepressant medications throughout the time of the JUMP study. The doses for antidepressants were converted into equivalent doses of imipramine (Inagaki and Inada, 2006). The number of depressive episodes, total duration of depressive episodes, and age at onset were confirmed via medical records. The retardation was defined as a score >1 on the HAM-D subscale item of "Retardation", and paranoid symptoms were defined as score >1 on the HAM-D subscale item of "Paranoid symptoms".

The present study was approved by the Medical Ethics Committee of Juntendo University, and was performed in accordance with the regulations outlined by Juntendo University. All participants provided written informed consent.

2.2. Follow-up evaluation

All participants were followed and evaluated for their clinical state. Depressive symptoms were assessed using HAM-D, and clinical remission was defined as state which maintained seven points or less on the HAM-D score (Frank et al., 1991) for at least 2 weeks. Mood-switching from depression to manic, hypomanic and mixed states was defined if the subject fulfilled the criteria for manic episode, hypomanic individual and mixed states on the DSM-IV. During the follow-up period, the patients who emerged with dementia ($n=4$), mild cognitive impairment (MCI, $n=2$), alcohol abuse ($n=3$), personality disorder ($n=3$), mental retardation ($n=1$), Parkinson's disease ($n=1$), or with an electroencephalogram (EEG) abnormality ($n=1$) were excluded from the present analyses. In addition, two patients withdrew consent to participate in the present study. Finally, the present JUMP study subjects consisted of 189 patients with MDD (75 males and 114 females; mean age, 55.9 years; age range, 21–85, 74 agitated patients and 115 non-agitated patients). The demographic and clinical information of the JUMP study subjects are presented in Table 1, and Fig. 1 presents the flow-chart of the participants.

2.3. Statistical analysis

We compared age, HAM-D score at hospital admission, age at onset, education, number of episodes, total duration of depressive episodes, HAM-D sub-scores (agitation, retardation and paranoid symptoms), duration of follow-up period, and maximum dose of daily antidepressants between the agitated and non-agitated patients using two-tailed unpaired student t-tests. Chi-square (χ^2) tests were used to compare the following variables: gender, retardation, paranoid symptoms, family history of mood disorder, medication with stabilizer (lithium or anticonvulsants), medication with antipsychotic agent, medication with tricyclic antidepressant (TCA), and mood-switching during follow-up period.

Analyses focused on incident mood-switching from depression to manic, hypomanic and mixed states. Kaplan–Meier survival curve and log-rank comparisons were used to compare time to mood-switching between agitated and non-agitated patients. Subjects were censored on period at remission of depression. We used Cox proportional hazards ratio estimates in a multivariate model to examine the relationship between the psychomotor agitation and risk of mood-switching. A significance level of $p<0.05$ was used. Statistical procedures were performed using the Japanese version of SPSS v15 (SPSS Japan Inc., Tokyo, Japan).

3. Results

3.1. Baseline characteristics of the present JUMP study subjects

Variables of gender, education, number of episodes, total duration of depressive episodes, and family history of mood disorder did not differ significantly between agitated and non-agitated patients. Agitated patients were significantly older ($p=0.01$) and older age at onset ($p=0.03$) had a significantly higher HAM-D score ($p<0.01$) and HAM-D sub-scores (agitation, retardation and paranoid symptoms) ($p<0.01$), higher frequency of retardation ($p<0.01$) and paranoid symptoms ($p<0.01$) when compared to non-agitated patients (Table 1).