Circadian Rhythm Characteristics in Mood Disorders: Comparison among Bipolar I Disorder, Bipolar II Disorder and Recurrent Major Depressive Disorder

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Objective: Morningness/eveningness (M/E) is a stable characteristic of individuals. Circadian rhythms are altered in episodes of mood disorder. Mood disorder patients were more evening-type than normal population. In this study, we compared the characteristics of M/E among the 257 patients with bipolar I disorder (BPD1), bipolar II disorder (BPD2) and major depressive disorder, recurrent (MDDR).
Methods: M/E was evaluated using the Korean version of the composite scale of morningness (CS). Factor analysis was done to extract specific elements of circadian rhythm (morning preference, morning alertness, and evening tiredness). The total score and scores for factors and individual items of CS were compared in order to evaluate differences among the three different diagnostic groups. Factor scores of CS were different among the diagnostic groups.
Results: BPD1 subjects had a higher score for evening tiredness than BPD2 subjects ($p=0.060$), and BPD1 subjects had a significantly higher score for morning alertness than subjects with MDDR ($p=0.034$). This difference was even more profound for the representative item scores of each factor; item 2 of CS for evening tiredness (BPD1>BPD2, $p=0.007$) and item 5 of CS for morning alertness (BPD1>MDDR, $p=0.002$). Total score of CS were not different among 3 diagnostic groups.
Conclusion: Circadian rhythm characteristics measured by CS were different among BPD1, BPD2, and MDDR. BPD2 showed more eveningness than BPD1. MDDR showed less morningness than BPD1. CS would be a reasonable endophenotype associated with mood disorders. More studies with large sample size of mood disorders on M/E are warranted.

KEY WORDS: Bipolar I disorder; Bipolar II disorder; Composite scale; Major depressive disorder; Chronotype.

INTRODUCTION

The regular rhythm of night and day regulates our life, as it does for most living organisms. Individual differences in the phases of human activity have long been considered and a continuum can be placed from morningness to eveningness. Diurnal preference is believed to be related to the phase of endogenous circadian rhythms.[1] Morningness/eveningness (M/E) variation measures are

associated with individual differences in the timing of physiological circadian rhythms in cardiovascular stress levels and core body temperature, as well as behavioral rhythms related to eating, exercise and performance.[2-4] Morningness and eveningness are heritable[5] and associated with circadian gene polymorphisms.[6,7] Recent genetic findings have demonstrated that some molecular mechanisms control circadian rhythms.[8]

Circadian rhythm hypotheses have been prominent in the explanation of major depressive disorder (MDD) and bipolar disorder (BPD). Various evidence provides support for an association between circadian rhythm dysfunction and mood disorder. Various phases of mood disorder (depressed, manic, episode prodrome, and interepisode periods) are associated with circadian rhythm abnormalities. Patients in the manic phase generally have a de-

creased need for sleep, and insomnia and hypersomnia are both commonly found in depressive patients.[9] Sleep disturbance is a common prodromal symptom of mania and is also seen in the prodrome of depression.[10] A relationship between depression and circadian phase delay has been suggested.[11] There seems to be a predisposition for circadian rhythm alteration in mood disorder patients. Sleep disturbances and instability of circadian rhythm continue when mood disorder patients are not acutely ill.[12-14] Since disruptions to circadian rhythms have been found among patients with MDD and BPD, interventions stabilizing circadian rhythms is recognized as therapeutic in consensus treatments of MDD and BPD.[15-17] Delayed circadian phase of melatonin secretion has been reported in euthymic bipolar and unipolar patients.[18]

It has been hypothesized that abnormalities in the molecular clock underlie the development of mood disorders.[19-21] Genes are considered to constitute an important etiologic factor in both mood disorders and circadian rhythm. Circadian gene polymorphisms are associated with symptoms of mood disorder in preclinical and human studies.[22-24] Although endophenotypes involved in mood disorder are largely unknown, M/E appears to be a good candidate.

The studies involving college students and adolescents have suggested that individuals with higher self-rated depression scores are more likely to be evening types.[25,26] Patients with MDD have been also reported to be significantly more evening type than controls.[27] Bipolar I disorder (BPD1) cases were more evening type than community based control individuals and cases with schizophrenia/schizoaffective disorder cases.[28] Other studies on BPD patients also suggest that BPD cases tended to be more evening-type than subjects in control groups and there were no significant differences in M/E scores between BPD1 or bipolar II disorder (BPD2) cases.[29] A study in Korea showed that adults with BPD1 had more evening patterns when compared with controls.[30] Thus, replicated evidence consistent with circadian phase alterations in MDD and BPD is now available. However, to our knowledge, no study has evaluated the differences in M/E variation among BPD1, BPD2 and MDD individuals.

BPD2 had more chronic and recurrent depressive episodes, while BPD1 had more severe episodes.[31] Because BPD2 does not seem to be more episodic than BPD1, we assumed that BPD1 patients and BPD2 patients would have different circadian rhythm characteristics. We considered the possibility that patients who had experienced only a single episode of MDD differed from those with MDD, recurrent (MDDR) in terms of circadian rhythm features. To get a more homogenous group for this study, we selected an MDDR group of patients with chronic and recurrent depressive episodes. In the present study, we compared the characteristics of M/E among BPD1, BPD2 and MDDR. The total score as well as factor scores and individual items of the M/E scale were analyzed in order to assess possible differences among mood disorders.

METHODS

Subjects

A total of 257 patients (male=77, female=180), with mood disorders participated in this study. These patients were recruited from the Eulji General Hospital and several psychiatric clinics in Seoul. There were 106 subjects with BPD1, 43 with BPD2, and 108 with MDDR; to be considered as eligible for inclusion in the study. The MDDR patient had to have experienced two or more separate major depressive episodes. Diagnoses were assigned to each patient according to the criteria in the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV). At least 2 different psychiatrists reviewed and discussed the psychiatric data, which included psychiatric interviews and Korean version of Mini International Neuropsychiatric Interview (K-MINI)[32] conducted by research nurses, and medical records. After reviewing the data, the psychiatrists reached a consensus on the final diagnoses of each patient. Subjects with a history of any kind of substance use, organic brain syndrome, or any general medical condition possibly manifesting as psychiatric symptoms were excluded from this study. All subjects participating in this study signed a written informed consent. The study protocol was approved by the ethics committees of both Eulji General Hospital and Seoul National University Hospital.

Measurement of Morningness/Eveningness

M/E was measured by pen and paper self-report questionnaires.[2] The composite scale of morningness (CSM) is a 13-item questionnaire which assesses individual differences in the time of day a person prefers to carry out various activities, and classifies people as morning-type or evening-type.[33] Previous studies have demonstrated good test-retest reliability and adequate external validity for the CSM.[34,35] The CSM has been translated into Korean and the Korean translation (i.e., CS) has been verified to have acceptable psychometric properties.[36,37] Three items are scored on a five-point scale from 1 to 5,

and the remaining 10 items are scored on a four-point scale, from 1 to 4. Higher scores indicate morning preference. Patients were asked to complete the CS and all the patients were done.

Statistical Methods

1. Factor analysis of CS

A principal component analysis (PCA) was conducted on the CS 13 items. The Kaiser-Meyer-Olkin measure (KMO) verified the sampling adequacy for the analysis (KMO=0.86). Barlett test of sphericity indicated that correlations between items were sufficiently large for PCA ($p < 0.001$). An initial analysis was run to obtain eigenvalues for each component in the data. We used Kaiser's criterion of retaining factors with eigenvalues greater than 1. Since factors were correlated with one another, promax rotation was performed to maximize the loading of each variable on one of the extracted factors and to minimize the loading on all other factors. SPSS-K ver. 12.0 (SPSS Inc., Chicago, IL, USA) was used for the analysis.

2. Comparisons among three diagnostic groups

Three different groups of mood disorders were compared for circadian rhythm characteristics. The three groups were BPD1, BPD2, and MDDR. First, we compared the age at interview and the age at onset of each diagnostic group using analysis of variance (ANOVA). *Post hoc* comparisons were performed with Tukey honestly significant difference tests (Tukey HSD) using SPSS-K 12.0. Since the mean age at interview was significantly different among patient groups and age is well known to be significantly correlated with CS scores, analysis of covariance (ANCOVA) was used to compare circadian rhythm characteristics among the three diagnostic groups

(BPD1, BPD2, MDDR) using age as a covariate. *Post hoc* comparisons were then performed to reveal any significant differences among the diagnostic groups. We analyzed the males and the females separately, since gender difference has been found in many aspects of mood disorder. The CS total score, factor scores, and individual item scores were investigated as circadian rhythm characteristics. All of the above analyses were performed with SPSS-K 12.0.

RESULTS

The mean age at interview among those with BPD1 was 38 years; it was 32 years for those with BPD2, and 56 years for those with MDDR. The groups differed significantly in terms of age at interview (ANOVA test, $p < 0.01$). Those with MDDR were significantly older than the other groups. The mean age at onset among those with BPD1 was 27 years; it was 24 years for those with BPD2, and 46 years for those with MDDR. The groups differed significantly in terms of the age at onset (ANOVA test, $p < 0.01$). The age of onset was significantly higher in those with MDDR than in the other groups. There was a preponderance of females in our sample (70.04% of the all subjects, Table 1).

The factor analysis on our sample found three factors structure for CS. They were morning preference, morning alertness and evening tiredness. These three factors explained 58.5% of the total variance of the CS total score; the main portion (37.54%) of variance was explained by the morning preference factor (Table 2). Morning preference was correlated with morning alertness and evening tiredness. However, morning alertness was relatively less correlated with evening tiredness.

Total scores of CS were significantly correlated with the age at interview in all the subjects (Pearson's r=0.293,

Table 1. Age at interview and age at onset of subjects (years)

	BPD1		BPD2		MDDR	
	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)
Total	106		43		108	
Age		37.75 (12.95)		32.09 (12.40)		55.73 (11.68)
Age at onset		26.74 (11.86)		24.08 (11.39)		45.60 (14.05)
Male	39		18		20	
Age		39.95 (13.42)		31.00 (14.54)		57.45 (16.59)
Age at onset		27.53 (12.97)		23.20 (11.74)		48.50 (17.24)
Female	67		25		88	
Age		36.48 (12.61)		32.88 (10.86)		55.34 (10.33)
Age at onset		26.27 (11.24)		24.71 (11.38)		45.67 (10.89)

BPD1, bipolar I disorder; BPD2, bipolar II disorder; MDDR, major depressive disorder, recurrent; SD, standard deviation.

Table 2. CS items and 3 factors

CS item number	CS items content	Factor 1 Morning preference	Factor 2 Morning alertness	Factor 3 Evening tiredness
11	Difficulty to rise at 6:00 a.m.	0.771	0.615	0.400
10	Time preferred to rise for a full day's work	0.752	0.432	0.340
9	Self-classification/assessment as morning or evening type	0.741	0.466	0.478
13	Level of morning or evening active individual	0.719	0.465	0.492
1	Time preferred to get up in morning	0.698	0.260	0.313
6	Physical exercise between 7:00-8:00 a.m.	0.582	0.470	0.042
8	Time of preferred peak performance for a test	0.554	0.101	0.146
4	The degree of alertness during the first half hour after waking up	0.344	0.860	0.165
5	The degree of tiredness during the first half hour after waking up	0.339	0.815	0.159
3	Ease of getting up in the morning	0.453	0.730	0.200
12	Time for recovery after rising from a night's sleep	0.520	0.529	0.113
7	Time when one feels tired in the evening as a need of sleep	0.378	0.184	0.885
2	Preferred time to go to bed in the evening	0.315	0.182	0.884
Initial eigenvalues		4.88	1.61	1.13
Eigenvalues after rotation		4.31	3.58	2.54
Variance (%)		37.5	12.3	8.6
Component correlation		Morning preference	Morning alertness	Evening tiredness
Morning preference		1.00	0.54	0.43
Morning alertness		0.54	1.00	0.24
Evening tiredness		0.43	0.24	1.00

Promax rotation was performed.
CS, Korean translation of composite scale of morningness.

Table 3. CS difference among BPD1, BPD2, and MDDR: male and female

	BPD1 Mean (SD)	BPD2 Mean (SD)	MDDR Mean (SD)	F	p value	Group comparison	p value
1	3.35 (1.20)	3.12 (1.33)	3.78 (1.15)	0.710	0.493		
2	3.04 (1.00)	2.44 (0.98)	3.24 (0.73)	4.769	0.009	BPD1 > BPD2	0.007
3	2.39 (0.89)	2.30 (0.67)	2.39 (0.89)	0.404	0.668		
4	2.16 (0.76)	2.05 (0.69)	2.00 (0.85)	2.232	0.109		
5	2.61 (0.78)	2.33 (0.78)	2.31 (0.86)	6.144	0.002	BPD1 > MDDR	0.002
6	2.70 (0.90)	2.63 (0.93)	2.62 (0.77)	0.253	0.777		
7	2.97 (0.99)	2.67 (0.92)	3.32 (0.86)	1.291	0.277		
8	2.62 (0.97)	2.53 (0.91)	2.87 (0.93)	0.964	0.383		
9	2.03 (1.02)	1.89 (0.85)	2.58 (1.08)	2.946	0.054		
10	1.94 (1.10)	1.88 (0.88)	2.15 (1.13)	0.293	0.747		
11	2.38 (1.09)	2.28 (1.00)	2.66 (1.03)	0.017	0.983		
12	3.00 (0.96)	2.93 (1.00)	2.93 (1.08)	0.752	0.472		
13	2.24 (1.02)	1.98 (0.96)	2.59 (1.03)	1.093	0.337		
Total score	33.42 (7.92)	31.02 (7.45)	35.44 (7.26)	0.721	0.487		
Factor 1	−0.14 (0.98)	−0.29 (0.97)	0.25 (0.98)	0.550	0.578		
Factor 2	0.12 (0.95)	−0.10 (0.91)	−0.08 (1.08)	3.308	0.038	BPD1 > MDDR	0.034
Factor 3	−0.09 (1.06)	−0.60 (1.02)	0.32 (0.80)	3.050	0.049	BPD1 > BPD2	0.060

Factor 1: morning preference, factor 2: morning alertness, factor 3: evening tiredness.
In case of significant difference among three diagnostic groups (BPD1, BPD2 and MDDR), *post hoc* comparisons were performed.
CS, Korean translation of composite scale of morningness; BPD1, bipolar I disorder; BPD2, bipolar II disorder; MDDR, major depressive disorder, recurrent; SD, standard deviation.

$p < 0.001$), and scores of two factors of CS were also significantly correlated with the age at interview in all the subjects (morning preference: Pearson's r=0.265, $p < 0.001$; evening tiredness: Pearson's r=0.388, $p < 0.001$).

CS scores for each diagnostic group are presented in Table 3. There was no significant difference in CS total score among the three groups. However there were significant differences in the factor scores of CS among the three groups. BPD1 subjects had a higher score of evening tiredness than BPD2 subjects (BPD1, −0.09 > BPD2, −0.60; p=0.060). BPD1 subjects had a significantly higher mean score than MDDR subjects in morning alertness

(BPD1, 0.12 > MDDR, −0.08; *p*=0.034). There were significant differences in specific individual item scores on CS among the three groups. There was a significant difference in the mean scores of item 2 (preferred time to go to bed in the evening) of the evening tiredness factor between BPD1 and BPD2 (BPD1, 3.04 > BPD2, 2.44; *p*=0.007). The mean score of item 5 (the degree of tiredness during the first half hour after waking up), a morning alertness factor, was significantly different between BPD1 and MDDR (BPD1, 2.61 > MDDR, 2.31; *p*=0.002) (Table 3). This difference was slightly more profound in the female subgroup than in the male subgroup (data not shown).

DISCUSSION

We found that circadian rhythm characteristics were different among mood disorders in this sample. BPD2 patients were more likely to experience evening tiredness than BPD1 patients and MDDR patients had less morning alertness than those with BPD1.

The correlation between age and CS was that older individuals tended towards morningness.[4] Children seemed to tend to morningness, but with age, the preferred time became progressively later, reaching a maximum in lateness at around 20 years of age, and then become earlier again with increasing age.[38] In our sample, total scores and the scores on morning preference and evening tiredness were also significantly correlated with age in the whole study population (data not shown).

In our study, individuals with BPD2 obtained lower scores than did those with BPD1 on all CS scales. Although the differences for total, factor and item scores did not reach statistical significance (except item 2), the tendency seemed clear. These data suggest that eveningness features are more highly associated with BPD2 than with BPD1. There have been studies showing evidence that BPD2 is different from BPD1, and that BPD2 is clinically even more complicated than BPD1 in many aspects. BPD2 patients experience longer depressive episodes, and more persistent residual depressive symptoms than BPD1 patients.[39] BPD2 patients spent a greater proportion of time in partial remission, and less time in full remission, though BPD1 patients had more severe episodes.[31,40] Depressive symptoms at syndromal or subsyndromal levels appear to be strongly associated with poor psychosocial functioning in BPD.[19,41] Additionally, it has been demonstrated that BPD2 patients exhibited a higher prevalence of premenstrual symptoms than the control individuals unlike BPD1.[42] These suggest that BPD1 and BPD2 are sufficiently distinct in terms of long-term course and distinctive subtypes with different clinical characteristics. The course of illness in BPD2 patients seems to be more chronic and less episodic. These findings provide strong support for the notion that BPD2 is more highly correlated with the eveningness characteristics of the circadian rhythm.

In this study, we found that patients with MDDR were less morning alertness than those with BPD1. However, individuals with MDDR obtained higher scores than did those with BPD1 on in the CS items (except item 6) corresponding with morning preference and evening tiredness factors. Although these differences for the total, factor and item scores did not reach statistical significance (except morning alertness factor scores and item 5), the tendency seemed clear. Our results suggest that more MDDR patients are subjectively tired in the morning than BPD1 patients. From this finding, it is reasonable to assume that individuals with MDDR resemble individuals with BPD2 in M/E. One possible explanation for this finding would be that MDDR patients seemed to be chronically ill like BPD2 patients. In addition, MDDR is a heterogeneous diagnosis on the current DSM-IV diagnostic criteria. It includes a diagnostic specifier for hidden bipolarity in MDD, emerging evidence for a conceptualization of hypomanic symptoms has been proposed.[43] The current DSM-IV diagnostic criteria for BPD2 fail to include milder but clinically significant bipolar syndromes. A significant percentage of these conditions are diagnosed by default on MDD criteria as chronic MDD or MDDR.[44-46] It is possible that some MDD patients have significant subclinical bipolarity. These results show that MDDR and BPD2 have similar characteristics with their clinical correlates.

Several limitations of this study should be noted. First, CS is a self-rating scale and scoring is based on subjective evaluations. Although patients were clinically stable, subsyndromal mood symptoms can also affect the subjects' attitude toward their own characteristics. However, we carefully selected for euthymic patients by assessing current mood status. Second, the relatively small sample size, and the differences among diagnostic groups in number of subjects and gender distribution means the study lacks sufficient statistical power. In particular, the BPD2 group consisted of only 41 subjects. This could reflect the relative rarity of diagnosis of BPD2 in clinical practice. It is suggested that BPD2 patients may present with different mood disorders such as dysthymic disorder or MDD de-

pending on the age of interview.[47] Third, we conducted multiple comparisons (i.e., CS factor-wise, CS item-wise, and gender-wise) to verify several possibilities about the complex features of CS among different mood disorders. However, the *p* values in this study were not corrected for multiple testing. This should be considered during interpretation of the results. Fourth, our sample was composed of only three diagnostic groups, and there was no control group. Therefore BPD patients could not be compared with screened control individuals like previous studies.[28-30] Further studies including collection of control subjects and additional analyses should be undertaken to explore this area further.

We used the CS total score, factor scores, and individual item scores to measure M/E features. In the present study, there were also no significant differences in the CS total scores between BPD1 or BPD2 patients. This result was consistent with that of a previous study.[29] Because CS addresses the complex features of the circadian rhythm, scores on three factors and scores on individual items were applied in further analysis. Especially item 2 seems to be representative for the factor of evening tiredness and item 5 seems to be representative for the factor of morning alertness. These items were found to be even more sensitive in catching differences between the disease groups.

It has been suggested that circadian rhythm characteristics could be an endophenotype of mood disorders. Endonphenotype is considered as a helpful link to find genes for disease because it is less complex in phenotypic manifestation and more likely to be controlled by small number of genes.[48] Especially for the BPD, circadian rhythm instability on sleep-wake cycle, body temperature and neuroendocrine profiles found to be associated.[10,49,50] Lithium's therapeutic effect on BPD might be brought from the lithium's effect on circadian cycles.[51] In this study, we found different CS factor scores among mood disorders. Taken all together, it is possible that CS, a stable and quantifiable measure reflecting circadian rhythm, would be a reasonable endophenotype associated with mood disorder. Investigations on genetic eiologies of mood disorder using CS endophenotype could be promising.

In conclusion, we found that different mood disorders had different circadian rhythm characteristics through comparing the factor scores and specific item scores of CS among BPD1, BPD2 and MDDR. BPD2 showed more eveningness than BPD1, and MDDR showed less morningness than BPD1. CS would be a reasonable endophenotype associated with mood disorders. More studies with large sample size of mood disorder on M/E are warranted.

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