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The association between biological rhythm and psychosocial functionality in patients diagnosed with bipolar disorder 1 and in healthy first degree relatives

Rhythm dysregulation and psychosocial functioning

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Abstract

Aim: Circadian rhythm dysregulation is one of the important mechanisms playing a role in the pathophysiology of bipolar disorder (BD). This study aims to examine the relationship between deterioration in circadian rhythm and psychosocial functionality among patients with BD, healthy first-degree relatives, and a control group.

Material and Methods: We planned a cross-sectional study consisting of 64 BD patients, 64 healthy first-degree relatives, and 64 healthy controls. We used the Biological Rhythms Interview of Assessment in Neuropsychiatry to assess disruption in circadian rhythm, the Morningness-Eveningness questionnaire to determine chronotypes, and the Functioning Assessment Short Test to assess functionality.

Results: In our study, it was found that the circadian rhythms of BD patients were more disrupted than those of the control group, while the BD group was found to exhibit higher rates of morningness and eveningness than patient relatives and healthy controls. It was determined that the circadian rhythms of BD patients with evening chronotype were more disrupted, whereas an association was noted between dysregulation circadian rhythm and deteriorated functionality in the patient group.

Discussion: In light of the obtained data, it can be suggested that circadian rhythm disorder in BD patients may be an independent predictor of low psychosocial functioning. Our study supports that therapeutic interventions targeting circadian rhythm stability play an important role in the acute and long-term management of BD.

Keywords

Bipolar Disorder, Chronotype, Circadian Rhythm, Psychosocial Functionality

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Introduction

Bipolar disorder is a chronic mood disorder characterized by recurrent manic, hypomanic, and depressive episodes [1]. BD is associated with cognitive and functional impairment and a decrease in quality of life. Rapid cycling, co-diagnosis of substance use disorder, sub-threshold depressive symptoms, and neurocognitive impairments are important factors affecting functionality [2]. However, there is still insufficient information on predictors of functional impairment.

In humans, the sleep-wake cycle, hormone levels, mood, and cognitive functions have a rhythm of approximately 24 hours, called the circadian rhythm, and are regulated by a central clock located in the suprachiasmatic nucleus (SCN) in the anterior hypothalamus [3]. While the SCN self-regulates approximately 24-hour rhythms, it is also synchronized by environmental cues. Light is the most important factor in terms of circadian rhythm, but it is also affected by many environmental factors and daily activities, meal times and social activities [4].

Chronotype is a concept that subjectively expresses the time when individuals feel best to carry out their daily activities and reflects the physiological order of the circadian system [5]. Different chronotypes have been defined for humans, including morningness and eveningness. Circadian preferences displaying both chronotype features are classified as intermediate types. This classification is based on the sleep-wake cycle as well as biological, psychological, and behavioral variables [3].

The pathophysiology of BD includes both endogenous abnormalities in the central clock, SCN, and disturbances in the external regulation of circadian rhythms by physical and social cues. In many studies, polymorphisms are found in genes related to circadian rhythm in BD patients, suggesting that circadian rhythm dysregulation may display familial characteristics [6]. Some studies report circadian rhythm disorders in people at risk for BD as well as an increased sensitivity to circadian rhythm dysregulations [7].

The risk of developing BD is known to be higher in first-degree relatives of patients with BD compared to the general population. It is emphasized that a family where a genetic disease is seen intensely share some common features, both in the patient and in the individuals who have susceptibility genes but who do not have the disease, which should be investigated [8]. The detection of circadian rhythm disorders during periods of remission, and its presence in healthy patient relatives has brought forward that this condition may be an endophenotype candidate for BD [7]. In BD, the detection of well-defined disease-related endophenotypes is important for the development of intervention strategies for these risk groups.

Our study aims to examine the relationship between deterioration in circadian rhythm and psychosocial functionality among BD-1 patients, healthy first-degree patient relatives, and a control group.

Material and Methods

Study Design and Participants

In our study, the patient group consisted of a total of 64 euthymic BD patients who applied to the Ondokuz Mayıs University Faculty of Medicine Psychiatry outpatient clinic, were hospitalized in the psychiatry ward, and were diagnosed with BD-1 according to DSM-5 [1]. The inclusion criteria for our study were determined as being between the ages of 18-65, having a score of 5 or less on the Young Mania Rating Scale, and having a score of 7 or less on the Hamilton Depression Rating Scale. First-degree relatives and healthy volunteers between the ages of 18-65 were included in the study. Those with any neurological disease or organic mental disorder, or those with alcohol or substance abuse were excluded. Those using any psychotropic drugs were excluded from the first-degree relatives and healthy controls group.

64 healthy first-degree relatives of the patient group and 64 healthy volunteers constituted the control group following their evaluation with respect to inclusion and exclusion criteria. 24 parents, 24 siblings and 16 children as healthy first-degree relatives were included in the study. A gender-matched control group was formed.

Data Collection Tools

Biological Rhythms Interview of Assessment in Neuropsychiatry (BRIAN)

It is an assessment tool consisting of 21 items with a four-point Likert type and is applied by the interviewer [9]. It consists of five subscales, which include sleep, activity, social, eating habits, and the dominant rhythm pattern. The Turkish validity and reliability study of the scale was conducted by Aydemir et al. in 2012. In the internal consistency analysis of the scale, Cronbach's alpha coefficient was calculated as 0.899 [10].

Morningness - Eveningness Questionnaire (MEQ)

The scale developed by Horne et al divides individuals into 3 groups: 'morning type', 'evening type' and 'medium type' according to sleep-wake pattern, lifestyle and performance duration [11]. The Turkish validity and reliability study was conducted by Pündük et al., and the Cronbach α internal consistency coefficient was calculated as 0.84 [12].

Functioning Assessment Short Test (FAST)

It is a 24-item, four-point Likert-type scale filled by the interviewer [13]. High scores indicate poor functionality. The Turkish validity and reliability study was conducted by Aydemir and Uykur in 2012, and the Cronbach α coefficient was found to be 0.960 [14].

Hamilton Depression Rating Scale (HAM-D)

It is an interviewer-filled scale developed to evaluate depression severity in patients diagnosed with depression [15]. Akdemir et al. conducted the Turkish validity and reliability study in 1996 and found the Cronbach α internal consistency coefficient to be 0.75 [16].

Young Mania Rating Scale (YMRS)

It aims to evaluate the severity and shifts of the manic state [17]. The Turkish validity and reliability study was conducted by Karadağ et al. in 2001, and the Cronbach α coefficient was found to be 0.79 [18].

Statistical Analysis

Study data were uploaded to the system and analyzed using SPSS for Windows 21.0 (SPSS Inc, Chicago, IL). Descriptive statistics were presented as mean (±) standard deviation, median (Q1-Q4), frequency distribution, and percentage. The conformity of variables to the normal distribution was examined using visual (histograms and probability graphs) and analytical

methods (Kolmogorov-Smirnov/Shapiro-Wilk Tests). Kruskal-Wallis and chi-square tests were used for group comparisons that did not fit the normal distribution. A one-way ANOVA test was used for group comparisons with a normal distribution. The relationship between the variables was examined with the Spearman correlation test. In the evaluation of the Spearman r coefficient, a relationship score of 0-0.3 was accepted as very low, a score of 0.3-0.5 as low, a score of 0.5-0.7 as moderate, a score of 0.7-0.9 as high, and a score of 0.9-1.0. Univariate and multivariate linear regression analyses were used for modeling. p<0.050 was accepted as statistically significant.

Ethical Approval

This study was approved by the Ethics Committee of Ondokuz Mayıs University (Date: 2021-05-28, No: 2021/257).

Results

The data of 64 patients diagnosed with BD-1, 64 first-degree relatives of BD-1 patients and 64 healthy volunteers were examined. The average age in the BD group was 36.2±10.7 years. It was observed that the patient's relative group (39.6±13.3) was statistically significantly older than the healthy controls (33.3±6.8) (F:5.089, p:0.007). There was no statistically significant difference between the groups in terms of gender. It was found that the healthy control group had a statistically significantly higher number of years of education than the BD and patient relative groups (KW:39.189, p:0.001). 87.5% (n: 56) of the BD group were in the antipsychotic group, 54.7% (n: 35) were in the lithium group, 45.3% (n: 29) were in the sodium valproate group, 14.1% (n: n: 9), in the antidepressant group, 4.7% (n:3) were using benzodiazepine and 3.1% (n:2) were using lamotrigine. 92.2% (n:59) of the patients were using combination treatments.

Comparison of the circadian rhythm dysregulation between the groups in the sleep subscale showed that the BD group displayed statistically significantly more deterioration than patient relatives and healthy controls, while healthy controls displayed statistically significantly more deterioration than patient relatives. Activity, social, eating habits, and total impairment scores were statistically significantly higher in the BD group than in the other two groups. Table 1 shows the comparison of circadian rhythm dysregulations between the groups.

Intergroup comparison of chronotypes demonstrated that the BD group displayed a higher rate of morning (39.1%) and evening (31.3%) chronotype features and a lower rate of intermediate type (29.7%) features than the patient relatives and healthy controls (x2:24.681, p:0.001).

Comparison of circadian rhythm dysregulation between the chronotypes in the patient group showed that the patients with the evening type chronotype had statistically significantly higher sleep scores than those with the morning and intermediate type chronotypes. Similarly, the social scores of patients with an evening chronotype were higher than those of patients with an intermediate type of chronotype. In terms of total scores, the evening type had the highest score, while the intermediate type had the lowest score. Table 2 shows the comparison of circadian rhythm dysregulations between chronotypes in the BD group.

A comparison of functionality between chronotypes in the BD group showed that the evening type displayed impairment at a significantly higher rate than the morning type in the autonomy subscale (KW: 8.669, p:0.013).

Comparison of the association between functionality and circadian rhythm dysregulation in the BD group revealed a relationship between total dysregulation and total functional impairment (r:0.485, p:0.001). Table 3 shows the association between functionality subscales and circadian rhythm dysregulation subscales.

Discussion

When the comparison was made between the groups, it was determined that patients with BD-1 had more circadian rhythm irregularities in all sub-dimensions compared to the relatives and healthy control groups. It was found that patients with BD were more sensitive to social rhythm disruptions caused by life

Table 1. Intergroup comparison of circadian rhythm dysregulation

	Bipolar Disorder (1) (n:64)	Patient relative -2 (n:64)	Healthy control -3 (n:64)	Statistics	p	Post-hoc
Sleep	10 (Q1:8- Q4:13)	7 (Q1:5- Q4:8)	8 (Q1:8- Q4:9)	KW: 44.085	0.001*	1>3>2
Activity	11 (Q1:8- Q4:13)	5 (Q1:5- Q4:8)	6 (Q1:6- Q4:7)	KW: 58.536	0.001*	1>2=3
Social	8 (Q1:6- Q4:9)	5 (Q1:5- Q4:7)	5 (Q1:4- Q4:6)	KW: 42.332	0.001*	1>2=3
Eating habits	9 (Q1:8- Q4:10)	6 (Q1:4- Q4:8)	6 (Q1:5- Q4:7)	KW: 65.976	0.001*	1>2=3
Total	38 (Q1:32- Q4:44)	23 (Q1:20- Q4:34)	26 (Q1:25- Q4:28)	KW: 67.551	0.001*	1>2=3

Note: Median and quantile values are presented. Post-hoc analyses were performed with the Kruskal-Wallis and one-way ANOVA tests, and Bonferroni correction was utilized. *p<0.017

Table 2. Comparison of circadian rhythm dysregulation between chronotypes in the bipolar disorder group

	Morning Type -1 (n:25)	Intermediate Type -2 (n:19)	Evening Type -3 (n:20)	Statistics	p	Post-hoc
Sleep	9 (Q1:8- Q4:10)	10 (Q1:8- Q4:11)	13 (Q1:12- Q4:14)	KW: 23.331	0.001*	3>1=2
Activity	10 (Q1:9- Q4:13)	8 (Q1:6- Q4:12)	12 (Q1:11- Q4:14)	KW: 5.999	0.050	
Social	7 (Q1:6- Q4:9)	7 (Q1:5- Q4:8)	8 (Q1:8- Q4:10)	KW: 9.997	0.007*	3>2
Eating habits	8 (Q1:7 Q4:10)	9 (Q1:7- Q4:10)	10 (Q1:10- Q4:11)	KW: 5.981	0.050	
Total	35 (Q1:31- Q4:40)	34 (Q1:28- Q4:39)	44 (Q1:44- Q4:48)	KW: 16.379	0.001*	3>1>2

Note: Median and quantile values are presented. The Kruskal-Wallis test and Bonferroni correction were performed. Post-hoc analyses were performed with a one-way ANOVA test. *p<0.017

Table 3. The association between functionality and circadian rhythm dysregulation in the bipolar disorder group

		Sleep	Activity	Social	Eating habits	Total irregularity
Autonomy	r	0.457	0.301	0.370	0.258	0.437
	p	0.001*	0.016*	0.003*	0.039*	0.001*
Professional functionality	r	0.137	0.297	0.330	0.247	0.301
	p	0.279	0.017*	0.008*	0.049*	0.016*
Cognitive functionality	r	0.252	0.145	0.221	0.216	0.255
	p	0.045*	0.254	0.079	0.087	0.042*
Financial matters	r	0.451	0.486	0.356	0.395	0.546
	p	0.001*	0.001*	0.004*	0.001*	0.001*
Interpersonal relations	r	0.367	0.376	0.389	0.247	0.425
	p	0.003*	0.002*	0.001*	0.049*	0.001*
Leisure activities	r	0.145	0.433	0.353	0.331	0.395
	p	0.254	0.001*	0.004*	0.007*	0.001*
Total functionality	r	0.351	0.427	0.453	0.351	0.485
	p	0.004*	0.001*	0.001*	0.004*	0.001*

Note: The Spearman correlation analysis was used

events, and the BD group experienced social rhythm disruptions at a higher rate following a life event of similar intensity compared to healthy controls [6]. Disruptions in activity, social, eating, and sleep rhythm patterns may persist as residual symptoms in individuals with BD even during remission [19]. Our findings were evaluated in accordance with the literature and indicate that there is a relationship between the pathogenesis of the disease and circadian rhythm dysregulation.

In our study, evening chronotype was found to be statistically significantly higher in our patient group than in the patient relatives and control groups. In the BD patient group, the rates of morning, evening, and intermediate chronotypes were found to be similar to each other. The intermediate chronotype is known to be the most common type in the adult population [20]. The higher incidence of morning and evening chronotypes in the BD patient group compared to control groups may be due to the fact that BD patients experience circadian rhythm alterations at a higher rate and may have difficulty regulating their circadian rhythms.

It was found that the sleep parameter of the patients with the evening chronotype was statistically significantly more disrupted than the other two groups. It can be said that exposure to outdoor light affects the entrainment stage of circadian rhythm, and evening chronotypes are disadvantageous in terms of sleep loss and poor sleep quality since our society has mostly synchronized programs according to the morning chronotype [21]. Individuals with the evening chronotype have been shown to be more likely to suffer from social jetlag, as they have to adjust their habits to social demands that are not compatible with their internal circadian rhythms [22]. Similarly, in our study, the social scores of the patients with the evening chronotype were higher than those with the intermediate chronotype, indicating that circadian rhythm disruption is more common in the evening chronotype. In addition, our finding that the evening chronotype had statistically significantly higher scores than the intermediate chronotype in total functionality scores in the bipolar group is also consistent with the literature [5].

In our study, a statistically significant relationship was noted between circadian rhythm irregularity and total impaired functionality scores in the BD patient group. A moderately strong correlation was found between total biological irregularity scores and functional impairment related to financial issues. A study examining the burden of BD reported that BD patients had a high unemployment rate and experienced occupational difficulties [23]. This may have caused the patients to experience difficulties in financial matters. In BD, both manic and depressive episodes have harmful and long-lasting effects on general functionality, occupational status, and job performance, while, on the other hand, the absence of a daily routine due to being unemployed can increase the risk of a mood episode recurring [24]. Also, consistent with social rhythm theory, life events may impair functionality by triggering subsyndromal depressive symptoms in BD patients, which is in line with studies on interpersonal and social rhythm reporting that regularity of daily and social rhythms reduces relapse and improves occupational functioning in BD patients [25].

Limitations and Strengths

Our study has some limitations. In our study, all participants in the patient group were receiving pharmacological treatment that has the potential to affect their circadian rhythms, especially their sleep patterns. Most patients with BD receive lifelong preventive treatment. Therefore, it is very difficult to obtain a sample of patients who are not on medication in order to exclude the effects and side effects of drugs. Additionally, sleep-related symptoms may remain as residual symptoms of bipolar disorder. This situation was not excluded in our study.

In terms of the strengths of our study, it is the first to investigate functionality among chronotypes in the relatives of patients with BD. A review of the literature shows that there are only a few studies examining circadian rhythm irregularities among patient relatives. The relatively high age level of our patient relatives enabled our control group to be more objective, in which individuals with disease-related genes but not clinical manifestations of the disease were targeted, in contrast to studies that included children of BD patients.

Conclusion

In conclusion, we observed that the circadian rhythms of BD patients in remission were more disrupted than in the healthy control group, and morning and evening chronotypes were observed more frequently in BD patients than in healthy control groups. We found that circadian rhythms were more disrupted in BD patients with an evening chronotype, and their functionality was worse than in patients with an intermediate chronotype. We detected a relationship between circadian rhythm irregularity and impaired functionality in BD patients. Our results suggest that the biological irregularity detected in BD patients may be an independent predictor of poor psychosocial functioning. Although longitudinal studies are needed to test the causality of such a relationship, our study supports the idea that therapeutic interventions targeting circadian rhythm stability play a significant role in the acute and long-term management of BD. Longitudinal studies with larger and multicenter sample groups in the future will also be useful in this regard.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some

of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and Human Rights Statement
All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or compareable ethical standards.

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Conflict of Interest
The authors declare that there is no conflict of interest.

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