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RESEARCH ARTICLE

Evaluation of broad autism phenotype and handedness in patients with bipolar disorder

Alparslan Cansiz[1], Bahri Ince[2]

[1]Selcuk University, Faculty of Medicine, Department of Psychiatry, Konya, Turkey
[2]Bakirkoy Prof. Mazhar Osman Training and Research Hospital for Psychiatry, Neurology and Neurosurgery, Prof. Timucin Oral Mood Disorders Unit, Istanbul, Turkey

ABSTRACT

Objective: Genome-wide association studies of psychiatric disorders have revealed a multiplicity of common genetic variants between bipolar disorder (BD) and autism. It has been established that the frequency of affective psychosis is greater in individuals with autism. However, studies of the frequency of autism spectrum symptoms and autism-related hand preference in patients with BD are limited. The aim of this study was to investigate the broad autism phenotype and dominant hand preference in BD patients.

Method: A total of sixty-six (thirty-three female) patients of the Bakirkoy Prof. Mazhar Osman Training and Research Hospital for Psychiatry, Neurology, and Neurosurgery mood clinic diagnosed with bipolar I disorder who were in a euthymic period and 66 healthy controls matched for gender, age, and years of education were enrolled in the study. Sociodemographic and clinical characteristics of the patients were obtained from patient records, and the Autism Spectrum Quotient test (AQ) and Edinburgh Handedness Inventory self-report screening tools were administered.

Results: The mean disease duration was 15.5±8.4 years and the mean age of onset was 21.3±5.1 years. The mean total AQ score was 22.9±4.9 in the patient group and 19.1±4.4 in the control group, which represented a statistically significant difference. The mean score for the AQ subscales of communication, imagination, and attention switching were also higher in the patient group, and the difference was significant. Regression analysis indicated that the presence of BD was predictive for a higher AQ score; gender and hand preference did not demonstrate predictive value related to the AQ score.

Conclusion: The results of this research indicated that the broad autism phenotype was common in BD. The broad autism phenotype should be kept in mind to better understand the clinical features of BD patients. Additional evaluation of the effect of the phenotypes including hand preference on the course of BD should be conducted in studies with larger samples.

Keywords: Autism spectrum disorders, bipolar disorder, broad autism phenotype, handedness

INTRODUCTION

Bipolar disorder (BD), characterized by manic and depressive episodes, affects approximately 1% of the population (1). The cause of BD has not yet been fully explained; however, important findings have suggested a genetic predisposition. In a recent meta-analysis of BD, the concordance correlation coefficient was found to be 0.81 in monozygotic twins and 0.49 in dizygotic twins (2). Although genetic factors play an active role in the etiology of BD, they are not the only influence. Obstetric complications, infections, childhood trauma,

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Correspondence: Alparslan Cansiz, Selcuk University, Faculty of Medicine, Department of Psychiatry, Konya, Turkey
E-mail: alpcan2861@gmail.com

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and adverse growth conditions in the postpartum period are neurodevelopmental factors that can contribute to the pathophysiology of BD (3). Early deterioration in cognitive abilities and a poorer prognosis have been reported in a patient group with significant neurodevelopmental factors (4).

Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by challenges with social behavior and communication, limited interests, and repetitive behaviors. The prevalence has been reported to be 1.9% in prospective cohort studies, and the incidence in men was 4 to 7 times higher than in women (5). As in other psychiatric conditions, it is a clinical manifestation that may be the result of several genetic and non-genetic factors (6). Genes thought to be related to the pathophysiology of autism have also been detected in other diseases. Recent extensive genome-wide association studies have shown that autism, schizophrenia, BD, major depressive disorder, and attention-deficit hyperactivity disorder share certain variants (7). ASD and BD are among the diseases with the highest concordance in monozygotic twins (2). It has been revealed in clinical trials that other psychiatric disorders are common in autism. Studies evaluating the frequency of BD in individuals with autism have noted comorbidities in a wide range of 4.4% to 37% (8). However, the potential for diagnostic confusion increases with the coexistence of autism and other mental disorders. In a study of a group of adults presenting with major depression, 11% of the patients were diagnosed with ASD (9). The inadequacy of existing diagnostic systems to accurately identify mood disorders in individuals with autism due in part to the commonality of risk factors and symptoms adds to the diagnostic challenge (10). The epidemiological data and diagnostic difficulties suggest that the possibility of ASD should be considered and evaluated in patients with BD and other mental disorders without a pre-existing autism diagnosis.

The reported incidence of autism has increased in recent years (11), however, recent studies have shown that autistic features can also be seen in healthy individuals (12,13). Mild autistic symptoms, such as modest social and cognitive impairment, differences in communication skills, extraordinary memory, limited behavioral patterns, narrow interests, the need to perform repetitive behaviors, and a predisposition to focus on details rather than the whole, referred to as the broad autism phenotype, can be found in genetic relatives of those with autism (14). The broad autism phenotype has been documented in the general population and various psychiatric disorders (15-17). BD research has determined the presence of broad autism spectrum characteristics in almost 1 of 2 patients (17-19). In the first and, to our knowledge, only study of this sort to be conducted in Turkey, 26.4% of BD patients were classified as demonstrating high levels of autistic traits, a rate higher than the abovementioned studies (20).

Atypical handedness is a clinical feature consistently seen in autism (21). Handedness other than a right-hand preference (left-, mixed-, non-right-handedness) is considered atypical handedness. It has been reported that approximately 10% of the general population has atypical handedness (22). Atypical handedness has been shown to be associated with prenatal testosterone exposure and may be a reflection of cerebral lateralization (21,23). Atypical handedness has been investigated in many psychiatric disorders, including BD (24-26). Atypical handedness has been found to be elevated in patients with psychiatric diseases in comparison with healthy controls (27). Further evaluation of atypical handedness may provide useful information for a holistic approach to the broad autism phenotype in BD.

In recent years, there has been increased attention on the relationship between broad spectrum of autism and BD. Investigation of neurodevelopmental features, such as the broad autism phenotype and hand preference, may contribute to a better understanding of the etiology and clinical correlates of bipolar disorder. This study was designed to evaluate autistic features commonly seen in BD patients and the relationship of these features to dominant hand preference and clinical characteristics.

METHOD

This study was approved by the Selcuk University Local Ethics Committee [IRB: 07.04.2021–2021/192]. The patients enrolled were informed about the study and provided written consent.

Study Sample

Patients who were treated at the Prof. Timucin Oral Mood Disorders Unit, providing specialized mental health care for patients with mood disorders within the Bakirkoy Prof. Mazhar Osman Training and Research Hospital for Psychiatry, Neurology and Neurosurgery, for a diagnosis of bipolar I disorder according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) diagnostic criteria were enrolled in the study. In all, sixty-six patients were consecutively selected from patients who presented for follow-up in

April 2021. The criteria for inclusion in the study were age of 18-65 and a euthymic period of at least 8 weeks. A score of ≤5 on the Young Mania Rating Scale and a score of ≤7 on the Hamilton Depression Rating Scale were accepted as evidence of a euthymic period. Patients with clinical conditions such as alcohol or other substance use disorder, mental retardation, or dementia, were not included in the study. The control group was formed of individuals matched according to age, gender, and education level from patients who presented at the psychiatry outpatient clinic for a required employment evaluation to determine the presence of no mental disorder.

After the clinical data of the research group were obtained from the hospital records, both the patient group and the control group were asked to complete the Autism Spectrum Quotient (AQ) and Edinburgh Handedness Inventory instruments.

Sociodemographic and Clinical Data Form

A semi-structured form was developed for this study by the researchers to record details such as age at disease onset, the severity of episodes, number of hospitalizations, presence of psychotic symptoms, suicide attempts, smoking habit, alcohol and other substance use, and family history of the disease.

Psychometric Scales

Hamilton Depression Rating Scale

The Hamilton Depression Rating Scale (HAM-D) is the most commonly used tool to assess depressive episode symptoms (28). The HAM-D is designed to be administered by clinicians after a structured interview. The scale consists of 17 items and a score 0-4 is given for each item. The score is used to evaluate the course of a depressive episode; a high score indicates greater severity. A validity and reliability study of the Turkish version of the scale was performed by Akdemir et al. in 1996 (29).

Young Mania Rating Scale

The Young Mania Rating Scale is a clinical interview scale is used to evaluate the severity and change of manic episodes (30). It consists of 11 items; 7 are assessed using a 5-point Likert type scale, and 4 are in assessed using a 9-point scale. A validity and reliability study of a Turkish version of the scale was performed by Karadag et al. in 2002 (31).

Autism-Spectrum Quotient

The AQ instrument was designed to identify adults on the autism spectrum and evaluate subthreshold autistic traits in healthy individuals. This self-assessment scale was the result of several years of studies using the American Psychiatric Association criteria and the findings of evidence-based cognitive abnormalities in autism. Baron-Cohen et al. (32) reported that an individual with normal intelligence capacity may exhibit autistic features and represent the broader autism phenotype. The scale uses a 4-point Likert-type scale and consists of 50 questions and 5 subdimensions: social skills, shifting attention, attention to detail, communication, and imagination. A higher score suggests greater evidence of the broad autism phenotype. Kose et al. (33) conducted a study of a Turkish version of the test and they calculated a test-retest reliability of 0.72 and an internal consistency coefficient as 0.64.

Edinburgh Handedness Inventory

Handedness was identified using the Turkish version of the Edinburgh Handedness Inventory (34) modified by Geschwind and Behan (35,36). The respondent is asked to identify which hand they prefer to use to perform daily activities, such as writing and using scissors or other utensils. The items are scored with +10, +5, 0, -5, -10 points for responses of "always right," "usually right," "two-handed," "usually left," and "always left," respectively. The value obtained, the Geschwind score (GS), is between +100 and -100. Following Geschwind's proposal, the laterality score take as the sum of all these scores, and no quotient was calculated. In memory of Norman Geschwind, this laterality score called the "Geschwind score" and this value is between +100 and -100.A negative score indicates a greater predisposition to left-handedness, while a positive score indicates a right-handed preference.

Statistical Analysis

IBM SPSS Statistics for Windows, Version 20.0 software (IBM Corp., Armonk, NY, USA) was used to perform the statistical analysis. Normality of the distribution of continuous variables was assessed using a histogram and confirmed with the the Kolmogorov-Smirnov test. Descriptive statistics were displayed as the mean±SD for continuous variables, and the number of cases and (%) for categorical variables. Pearson's chi-squared test was used to compare categorical variables between the 2 groups. Student's t-test was used to compare the means of the 2 groups when the parametric test assumptions were met, and the Mann-Whitney U-test was used when the parametric test assumptions were not met. The independent effects of different predictors of the

Table 1: Sociodemographic data

	BD (n=66)		Control (n=66)		χ^2/t	p
	n*	%*	n*	%*		
Gender						
Female	33	50	33	50	0	1
Male	33	50	33	50		
	Mean+	SD+	Mean+	SD+		
Age (years)	36.7	9.8	37.7	8.1	-0.668	0.505
Education (years)	12.8	2.3	12.4	2.9	0.797	0.427
	n*	%*	n*	%*		
Marital status						
Married	32	48.5	38	57.6	1.964	0.375
Single	29	43.9	26	39.4		
Divorced	5	7.6	2	3		
Occupational status						
Housewife	7	10.6	7	10.6	2.646	0.266
Employed	44	66.7	51	77.3		
Unemployed	15	22.7	8	12.1		

*: Chi-squared test, +: Student t-test, p<0.05. BD: Bipolar disorder

AQ total score were examined using a multivariate linear regression model. A dummy variable was assigned for the categorical parameters used as an independent variable (female=0, male=1 for gender; no disease=0, present=1 for bipolar disorder). Cases with a type-1 error level <5% were considered statistically significant.

RESULTS

In all, 66 (33 female, 33 male) patients with BD and 66 gender-matched healthy controls were included in the study. The mean age of the patients was 36.7±9.8 years with a mean level of formal education of 12.8±2.3 years. The mean age of the control group was 37.7±8.1 years, with a mean education level of 12.4±2.9 years. There was no statistically significant difference between the groups in either parameter. The sociodemographic data of the sample are summarized in Table 1 and the clinical parameters of the patients with BD are presented in Table 2.

The mean total AQ score of the patients was 22.9±4.96 and 19.1±4.43 in the control group; the difference was significant (t=4.627; p<0.001). Evaluation of the AQ subscores of communication, imagination, and attention shifting indicated that the mean subscore of the patient group was higher than that of the control group, and that the difference was significant. Although other AQ subscores and the mean Edinburgh

Table 2: Clinical parameters of the BD group

	BD (n=66)	
	Mean	SD
Disease duration (years)	15.47	8.44
Age of disease onset (years)	21.3	5.1
Number of hospitalization	2.16	1.98
	n	%
Psychotic episode		
Yes	50	75.8
No	16	24.2
Suicide attempt		
Yes	18	27.3
No	48	72.7
Family history of psychiatric disorder		
Yes	24	36.4
No	42	63.6
Current treatment		
Lithium	16	24.2
Valproate	16	24.2
Lithium+valproate	5	7.6
Lithium+antipsychotic	16	24.2
Valproate+antipsychotic	9	13.6
Antipsychotic	3	2.3
Lithium+antidepressant	1	1.5

BD: Bipolar disorder

handedness score was higher in the patient group than in the control group, however, the difference was not statistically significant. The comparison of scale scores is summarized in Table 3. The handedness score was negative in 7.6% (n=5) of the BD group and 12.1% (n=8) of the control group; the difference was not statistically significant (χ^2=0.768; p=0.381).

Multivariate linear regression analysis was performed to assess the effect of the handedness score, BD presence, and gender on the AQ total score. A dummy variable (0 for female gender, 1 for male gender; 0 for the control group, 1 for the BD group) was assigned for the categorical variables of gender and the presence of BD. The analysis revealed that the independent variable of BD accounted for 15% of the AQ variance: (F[3,128]=8.474; p<0.001; R2 adjusted=0.15). A summary of the model is presented in Table 4.

DISCUSSION

Our results indicated a greater presence of the broad autism phenotype among BD patients than healthy controls. The difference was illustrated by reduced scores on the subfeatures of communication, imagination, and attention. In addition, broad autism phenotype traits were found to be a disease-related feature in BD patients, regardless of gender.

Although high rates of the broad autism phenotype have been reported in studies of mood disorders, to our knowledge, only 1 study included a control group (17). Among a total of 290 subjects, the authors of that study examined 56 BD patients and 65 healthy controls. A study that examined autistic traits using the results of the Social Responsiveness Scale-Second Edition found that 50% of the patients had autistic traits; however, an important limitation of the study is that the control group was not matched by gender. The significantly greater number of women in the control group (72% vs 56%) may have had an effect on the difference in the results (17). Dell'Osso et al. (18) studied the clinical significance of autistic traits in patients with BD. Their study examined 147 BD patients: 97 had been diagnosed with Bipolar 1 disorder and the remainder with Bipolar 2 disorder, but there was no control group. Similar to our findings, the patient group scored an average of 21 points on the AQ, and no significant difference was found based on gender (18). Aker et al. (19) found that male patients with BD had more autistic characteristics

Table 3: Comparison of scale scores

	BD (n=66)		Control (n=66)		Z/t	p
	Mean	SD	Mean	SD		
Autism-Spectrum Quotient						
Social skills*	4.68	2.02	4.35	1.88	-0.505	0.505
Communication*	4.2	1.71	2.53	1.25	-5.718	<0.001
Imagination*	4.5	1.99	3.42	1.74	-2.927	0.003
Attention to detail*	4.45	2.3	4.36	2.16	-0.219	0.827
Attention switching*	5.08	1.92	4.45	1.9	-2.060	0.039
Total AQ score#	22.91	4.96	19.12	4.43	4.627	<0.001
Edinburgh Handedness Inventory						
Geschwind score*	76.82	40.02	64.32	48.22	-1.650	0.099

*: Mann-Whitney U test, #: Student t-test, p<0.05. AQ: Autism-Spectrum Quotient, BD: Bipolar disorder

Table 4: Multivariate linear regression analysis for AQ total score

Model	Unstandardized coefficients		Standardized coefficients	t	p	95.0% Confidence interval for B	
	B	SE	Beta			Lower bound	Upper bound
(Constant)	17.748	0.928		19.125	<0.001	15.912	19.585
Edinburgh Handedness Inventory score	0.017	0.009	0.146	1.795	0.075	-0.002	0.035
Male sex	0.610	0.813	0.061	0.750	0.455	-1.000	2.219
BD presence	3.580	0.821	0.355	4.359	<0.001	1.955	5.206

Dummy variables were assigned for gender (female=0, male=1) and for BD presence (no=0, yes=1). AQ: Autism-Spectrum Quotient, BD: Bipolar disorder

than female patients, whereas, Yildiz et al. (20) and others have reported no relationship between gender and the presence of broad autistic traits. Congruent with most studies in the literature, we observed no significant difference in the AQ scores based on gender (37,38). Despite the methodological differences of earlier studies, the high detection of major autistic features in BD patients is consistent with the results of earlier genetic and clinical studies. Research examining the etiological relationship between BD and autism reveals common factors, including genetic, cognitive, social, and neurobiological processes (10). These processes are thought to have an influence on the broad autism phenotype in BD. It should therefore be kept in mind that the broad autistic phenotype may be the rule, rather than the exception, in patients with BD.

We located no study comparing subfeatures of AQ in BD patients with healthy controls. Studies evaluating subscales of AQ generally highlight 3 subfeatures (reduced communication, attention to detail, and social skills) (39). However, Hurst et al. (40) also noted high imagination scores. In our patient group, reduced social communication, imagination, and ability to shift attention stood out as prominent autistic features. Social communication requires advanced theory of mind (ToM) skills, as well as pragmatic language use (41). ToM is an individual's ability to grasp and describe mental states such as beliefs, intentions, and emotions in themselves and others. It has been shown that BD patients may have impairments in the use of pragmatic language in (42), and ToM may be particularly important to social communication. ToM skills develop in childhood and become increasingly complex (43). Many studies of BD patients have revealed impaired ToM (44). This weakness increases during an active disease period as well as over time (45,46). In both autistic and non-autistic clinical samples, it has been shown that social communication was weaker with impairment of ToM (47,48). It appears that impaired social communication, an autistic phenotype measure, may be a reflection of impaired ToM in BD patients.

Imagination is a complex mental activity that involves episodic memory retrieval, visualization, mental stimulation, spatial navigation, and thinking about a future event (48). It is a constructive process controlled by the default mode network (49). In BD, imagination is generally evaluated on the axis of creativity. Although increased creativity in BD has been reported for many years, methodological criticisms have been raised regarding the validity of the evidence (50). It has been suggested that increased imagination affects creativity, especially in a period of hypomania (50). This point of view posits that imagination becomes elevated in a dysfunctional way in psycho-emotional disorders (51). Findings regarding imagination in autism seem to indicate that higher cognitive function could have a critical role in distinguishing between autism and psychotic disorders (52). Imagination deficits in autism are a diagnostic criterion in the DSM-5 (53). Studies evaluating creativity in individuals with subclinical autistic traits, however, have yielded contradictory findings. It has been reported that personality-linked creativity was negatively associated with the broad autism phenotype, while cognitively-related creativity was not (54). Paola et al. (55) reported a negative relationship between personality-linked creativity and imagination scores in individuals with autism. The relationship between imagination and creativity in individuals with autism is not yet clear, and the relationship becomes even more complex in BD patients with autistic features. Studies with larger samples are needed to further examine our findings that imagination was low in BD patients. In addition, the extent to which creativity is affected in BD patients with a pronounced autistic phenotype should also be investigated in future studies.

It is well-known that BD patients typically experience attention-related problems, an indication of cognitive function (56). Although attention-deficit disorder is more common in periods of mania and depression, it has also been shown to occur in euthymic periods (57). Being easily distracted is one of the DSM-5 diagnostic criteria for a mania episode (53). The clinical model for attention identifies 5 subprocesses: focus, maintaining and shifting attention, selective attention, and divided attention (58). Shifting attention refers to the ability to direct attention to prioritized stimuli. Like other cognitive abilities, it begins to develop in the early years of childhood and matures in early adolescence (59). Studies of BD have generally focused on maintaining attention; the ability to shift attention has not been as thoroughly examined (57,60). In a study evaluating the ability to shift attention that used the dichotic listening test, the results indicated that the ability to shift attention was as impaired in BD patients as in schizophrenia patients (61). The ability to shift attention has also been explored in mood disorders in relation to reward stimuli. A study of reward responsiveness revealed that depression developed in 81 of 531 adolescents who were followed up for 9 years. The authors recommended efforts to improve responsiveness to reward stimuli and the ability to shift attention from

negative stimuli (62). Similarly, in a study evaluating patients with autism and BD in terms of reward expectancy, it was shown that cognitive impairment contributed to the decrease in reward expectation in both diseases (63). We also noted that decreased ability to shift attention in BD patients may be a result of impaired ability to shift attention to a reward. However, additional, more comprehensive research is required to better understand the ability to shift attention in BD patients and to reveal its relationship to the broad autistic phenotype.

Studies that have assessed handedness in BD have generally found that non-right-handedness is common, however, the methodological differences are striking. Although atypical handedness was common in 2 studies with large samples, the research did not include a control group (26,64). In another study without a control group, atypical handedness was determined based on only a single question (27). Fasmer et al. (65) used both adult and adolescent patients in the BD group, and a significant difference was found only in adolescent patients compared to a control group.

Consistent with our findings, other research has demonstrated no significant difference in handedness in a comparison of BD patients and healthy controls (25). Although hand preference typically develops in the first 2 years of life, it can change as a result of environmental or social effects and this constitutes an important obstacle to studies evaluating handedness (66). In a study conducted in Turkey found a significant relationship between coronary artery and cerebral functional dominance and the authors noted that a socially more acceptable view of right-handedness could affect hand preference (67). In our study, the prevalence of negative score of handedness in the patient group (7.6%) was lower than that observed in other countries (26,65). Social attitudes may have affected our results. In addition to environmental factors, the FOXP2 gene, which is known to be associated with language development, has been shown to influence hand preference (68). Inhibition of DISC1 promoter activity by the FOXP2 gene and DISC1 regulation of the GSK3B/catenin pathway has been associated with BD and other psychiatric diseases (69). There may be a relationship between BD and the genetic background of handedness. All of these results suggest that hand preference, which is regarded as an indicator of cerebral lateralization, should be further evaluated with a larger sample and strong methodology in BD patients.

Although atypical handedness has frequently been demonstrated in autism (21), we know of no study evaluating an association with the broad autistic phenotype. We observed a weak correlation between hand preference scores and the autistic phenotype, which may seem unexpected. The effect of environmental factors on hand preference is the first option that comes to mind to explain this finding; however, the regression analysis conducted showed that although hand preference demonstrated no predictive effect on the total AQ score, the p value obtained was close to the level of significance p=0.075). The relationship may have been affected by environmental factors or our sample size. Additional, larger studies are needed to further explore the significance.

Advanced analysis also revealed that gender was not a predictive value for the total AQ score. The literature offers conflicting data related to the assessment of gender and AQ scores. The male predominance in autism suggests that there may also be a gender difference in the broad autistic phenotype. It has been reported that the broad autistic phenotype is more common in males in the general population (70). However, studies of patients with schizophrenia and autism have shown that gender had no effect on the AQ score (37, 38), which is congruent with our findings; gender had no effect on the AQ score in our regression model.

Our study has some limitations. We used a relatively small sample compared with some previous studies, however, the inclusion of a control group and equal gender distribution is some compensation and provides useful new data. It should also be kept in mind that patients recruited from a specialized mood disorder center may not reflect all patients with BD. Finally, the use of self-report scales, especially to evaluate handedness, may have created a bias in the participant responses.

In conclusion, the increasing attention given to the broad autism phenotype in BD needs to be evaluated in conjunction with the AQ and other clinical phenomena. At this stage, study differences, such as sample selection and the screening tool used, make it difficult to obtain or assess common results. However, it has been proposed that the broad autistic phenotype is common in BD patients and our study findings confirm this conclusion. We think that the reduced abilities related to social communication, shifting attention, and imagination, which are symptoms of the broad autistic phenotype, that we detected in BD patients may be related to some previously described traits of autism spectrum. The evaluation of AQ subfeatures in BD patients will contribute to a better holistic understanding of these patients. Our finding that atypical handedness, another important individual feature associated with

autism, was not higher in the BD patient group than in healthy controls, is similar to some previous studies of BD patients, but we must also consider the potential role of social factors. We believe that additional testing with larger samples will contribute valuable information to the diagnosis and treatment of BD patients.

Contribution Categories		Author Initials
Category 1	Concept/Design	A.C., B.I.
	Data acquisition	B.I.
	Data analysis/Interpretation	A.C., B.I.
Category 2	Drafting manuscript	A.C.
	Critical revision of manuscript	B.I.
Category 3	Final approval and accountability	A.C., B.I.
Other	Technical or material support	A.C., B.I.
	Supervision	N/A

Ethics Committee Approval: This study was approved by the Selcuk University Local Ethics Committee [IRB: 07.04.2021–2021/192].

Informed Consent: The patients enrolled were informed about the study and provided written consent.

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