

## Affective Temperament Profiles in Patients with Multiple Sclerosis: Association with Mood Disorders

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### ABSTRACT

**Introduction:** The aim of the present study was to screen for bipolarity and to investigate the affective temperaments of patients with multiple sclerosis (MS) and the possible association between the clinical and demographic characteristics of MS patients and temperament profiles.

**Methods:** A total of 65 patients with MS and 66 healthy volunteers completed the 32-item hypomania checklist (HCL-32), the Mood Disorder Questionnaire (MDQ), and the Temperament Evaluation of Memphis, Pisa, Paris, and San Diego-Autoquestionnaire (TEMPS-A) tests. The HCL-32, MDQ, and TEMPS-A scores were compared between the patients and healthy volunteers.

**Results:** MS patients had significantly higher scores for the depressive, cyclothymic, irritable, and anxious domains of the TEMPS-A scale than the control group, whereas relapsing remitting MS (RRMS) patients had higher MDQ and TEMPS-A hyperthymia scores than secondary

progressive MS patients. MS patients who were being treated with interferon beta 1-b therapy had significantly higher MDQ scores than those being treated with interferon beta 1-a, glatiramer acetate, or who were without medication. Expanded Disability Status Scale (EDSS) scores were positively correlated with TEMPS-A depressive and hyperthymic temperaments.

**Conclusion:** Our results suggest that higher scores for affective temperament in MS patients indicate subclinical manifestations of mood disorders. Higher hyperthymia scores and manic symptoms detected in the RRMS group could shed light on the relationship between bipolarity and MS. Thus, the screening of bipolarity and affective temperament profiles in MS patients could help clinicians predict future mood episodes and decrease their impact on disease severity.

**Keywords:** Affective temperament, bipolarity, multiple sclerosis

### INTRODUCTION

Multiple sclerosis (MS) is a progressive and disabling disease that can seriously affect the quality of life (1). It is characterized by immune system attacks on the myelin sheath around axons in the central nervous system, causing various symptoms such as vision loss, muscle weakness, bladder control disturbance, numbness, fatigue, impaired cognitive function, and neuropsychiatric disorders (2).

Neuropsychiatric impairment has been reported as a common feature of MS (3). The most common psychiatric disorders in MS patients are mood disorders, particularly depression (4). The prevalence of depression for MS varies between 27% and 50% (5). In addition, several neuropsychiatric syndromes, such as anxiety disorders, bipolar disorder (BD), euphoria, pathological laughing and crying, psychosis, and personality disorders (PD), are also reported among patients with MS (6,7,8,9). Hence, an early diagnosis and treatment of these psychiatric symptoms could play an important role in the prognosis and quality of life in MS patients, considering that psychiatric symptoms are more common than other neurological disorders (10,11). However, few studies have evaluated the personality and temperament dimensions or the co-occurrence of BDs with MS (12,13,14,15,16).

There are a few studies that have focused on personality characteristics in MS patients using different screening tools for mood disorders. Several chronic medical disorders are associated with mood disorders, and it has also been hypothesized that immune and neurodegenerative diseases may cause increased neuronal oxidative stress, which can lead to pathological processes in the brain area that affect the emotions in BDs (17). Carta et al. (18) evaluated the risk of BDs for MS patients and stated that a lifetime prevalence of manic/hypomanic episodes, DSM-IV bipolar, and major depressive disorders was higher in MS patients than in healthy controls. Previous studies have also emphasized that a lifetime prevalence of BD is more frequently seen in MS patients; however, the association between these two disorders has not been fully determined (19,20).

Temperament as a heritable phenomenon describes the underlying biological and genetic tendencies of the personality and provides the automatic emotional response to events such as establishing an individual's activity level, rhythms, mood, and related cognitions types. Affective temperaments are thought to be subclinical forms of BDs (21). Akiskal et al. (22) identified five types of affective temperaments: depres-



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sive, hyperthymic, cyclothymic, irritable, and an anxious type known as the Temperament Evaluation of Memphis, Pisa, Paris, and San Diego-Autoquestionnaire (TEMPS-A).

The aim of this study was to evaluate (hypo)manic symptoms and affective temperaments and their relation with the clinical and demographic characteristics in patients with MS. Our main hypothesis was that (hypo) manic symptoms are more common in MS and that mood disorder questionnaires (MDQs) and affective temperament scores would be higher than in a control group. Besides, there is a relation between bipolarity and affective temperament that has an impact on disease severity in MS.

## METHODS

### Subjects

Sixty-five clinically definite MS patients who were recruited into the study were diagnosed with the Mc-Donald criteria (23). Patients with hepatic disorders, renal disorders, or who had received corticosteroid therapy within 3 months prior to testing were excluded. The demographic and clinical data of the patients were documented.

Sixty-six age- and sex-matched volunteers were enrolled as control subjects who had no medical or psychiatric disorders. The 32-item hypomania checklist (HCL-32), MDQ, and TEMPS-A tests were applied to all subjects.

### Measures

#### HCL-32

HCL-32 included 32 yes/no questions to identify hypomanic symptoms with depressive episodes for diagnosing BDs. The standard cut-off points have been reported to be a score of 14 or higher for HCL-32 (24).

#### MDQ

The MDQ was identified by Hirschfeld et al. (25) to assess the history of hypomanic or manic symptoms and to screen for BDs. The first part consists of 13 (yes/no) questions that screen for a lifetime history of hypomanic symptoms. The second part evaluates if two or more symptoms have been seen at the same time, while the last part asks for the results of the symptoms reported in the first part. Konuk et al. (26) performed the validity and reliability of the Turkish version of the MDQ. The optimal cut-off points have been reported to be a score of 7 or higher for MDQ and 14 or higher for HCL-32. "Positive scores" that show a high probability of a mood disorder are considered if scores are higher than the cut-off point ( $\geq 14$ ) for the HCL-32 and MDQ ( $\geq 7$  positive answers on the first item and yes answer for the second item) (27).

#### TEMPS-A

The TEMPS-A is a self-reporting questionnaire consisting of 110 items to measure five affective temperaments that define depressive, cyclothymic, hyperthymic, irritable, and anxious symptoms (5). Vahip et al. (28) performed the validity and reliability study of the Turkish version of the TEMPS-A.

#### Statistical analysis

All the data were analyzed using the Statistical Package for the Social Sciences version 19.0 (SPSS for IBM, Armonk, NY, USA). The normality of distribution in the groups was determined by the Kolmogorov-Smirnov test. Data were shown as the mean  $\pm$  standard deviation (SD). Differences between the groups were assessed by the Mann-Whitney U and

Student's t-tests for non-parametric or parametric values, respectively. Correlations between data were analyzed using Pearson and Spearman correlation tests. A p value  $<0.05$  was considered statistically significant.

## RESULTS

### Demographic and clinical data of the patient group

In this study, 70.8% ( $n=46$ ) of the patients were female and most were married (78.5%,  $n=51$ ). The mean age was  $37.8 \pm 7.7$  years. Their educational status was classified as follows: primary 26.7% ( $n=17$ ), high school 38.5% ( $n=25$ ), or college 35.4% ( $n=23$ ). The mean duration of the disease was  $6.52 \pm 5.1$  years. When we analyzed the clinical subtype of MS, the sample consisted of two different groups: relapsing remitting (75.4%,  $n=49$ ) and secondary progressive (24.6%,  $n=16$ ). The mean Expanded Disability Status Scale (EDSS) score was  $2.07 \pm 2.3$ . There were statistically significant differences between the EDSS scores of relapsing remitting MS (RRMS) patients and of secondary progressive MS (SPMS) patients (the mean EDSS scores for RRMS:  $1.041 \pm 1.31$ ; for SPMS  $5.25 \pm 1.80$ ;  $p < 0.001$ ). When the patients were evaluated with respect to treatment: 14 (21.5%) patients were on interferon beta 1-a (30  $\mu\text{g}/0.5$  MI) once a week, 16 (24.6%) patients were on interferon beta 1-a with a dosage of 44  $\mu\text{g}$  three times per week, 18 (27.6%) patients were on interferon beta 1-b (9.6 MIU) every other day, 12 (18.5%) patients were on glatiramer acetate (20 mg/mL) once a day, and 5 (7.7%) patients were medication free.

### Comparison of the MDQ and temperament scores between the patient and the control groups

There were no statistically significant differences between the groups with respect to gender ( $p=0.49$ ) and age ( $p=0.69$ ).

The proportion of patients with a positive MDQ score was 18.5% ( $n=12$ ) and 63.1% ( $n=41$ ) for the HCL-32 score. In addition, 12.3% ( $n=8$ ) of the patients had positive scores for both MDQ and HCL-32.

The mean TEMPS-A scores of the patients were  $8.9 \pm 4.3$ ,  $8.4 \pm 4.8$ ,  $7.9 \pm 4.8$ ,  $5.0 \pm 4.3$ , and  $8.4 \pm 5.8$  for the depressive, cyclothymic, hyperthymic, irritable, and anxious temperament domains, respectively.

Comparison of the TEMPS-A scores between the groups revealed significantly higher scores for the depressive, cyclothymic, irritable, and anxious domains in MS patients than in the control group ( $p=0.002$ ,  $p=0.011$ ,  $p=0.033$ ,  $p=0.002$ , respectively). There were no significant differences for the MDQ, HCL-32, and TEMPS-A hyperthymic scores between the groups ( $p=0.2$ ,  $p=0.6$ ,  $p=0.8$ ) (Table 1,2).

### Comparison of the MDQ and temperament scores according to the clinical factors in the patient group

For the MS patients, there was a significant difference in the MDQ and TEMPS-A hyperthymic scores in the relapsing remitting type compared with the secondary progressive type ( $p=0.035$ ,  $p=0.036$ ) (Table 3).

Comparisons following treatment of the MS patients for all the scales indicated that the patients who were on interferon beta 1-b had significantly higher MDQ scores than those who were on interferon beta 1-a and glatiramer acetate or who were without medication, but not the interferon beta 1-a 3 group ( $p=0.023$ ,  $p=0.006$ ,  $p=0.27$ ,  $p=0.198$ , respectively).

EDSS scores were found to be positively correlated with TEMPS-A depressive and hyperthymic scores ( $p=0.046$ ,  $r=0.249$ ;  $p=0.011$ ,  $r=-0.312$ , respectively) (Table 4).

No correlation was found between disease duration and the scores.

## DISCUSSION

This is the first study screening both the affective temperament and bipolarity of MS patients using TEMPS-A, HCL-32, and MDQ. We found higher scores for TEMPS-A depressive, cyclothymic, irritable, and anxious domains in MS patients than in the control group. Higher MDQ and TEMPS-A hyperthymic scores were found in MS patients for the relapsing remitting type than for the secondary progressive type. In addition, patients who were on interferon beta 1-b treatment had significantly higher MDQ scores than those taking interferon beta 1-a or glatiramer acetate or who were without medication.

There are a few studies in the literature on the personality characteristics of MS patients. For instance, Benedict et al. (28) evaluated the personality traits in MS patients using both the NEO Personality Inventory and the Hogan Empathy Scale, and they also investigated the relationship between cognitive dysfunction and personality change. MS patients presented slightly higher neuroticism and lower extraversion and conscientiousness than healthy controls. The reported also indicated that low conscientiousness was a risk factor for cognitive impairment in MS patients.

In another study, Fazekas et al. (30) investigated the temperament characteristics of MS patients with clinically isolated syndrome and RRMS patient scores using the Temperament and Character Inventory (TCI-125) scale. They found that higher scores of harm avoidance temperament were significantly associated with the increased lesion load per years of disease duration in their study. Another study was performed by Gazioglu et al. (31) to determine the personality traits of MS patients using the TCI-125 scale, and they found increased harm avoidance and decreased self-directedness (SD) scores among MS patients compared with the controls. Previous studies indicated that higher HA and lower SD scores are associated with neuroticism and depression (32).

Although depression is one of the most common psychiatric manifestations in MS, there is still limited data concerning BD and MS coexistence. There are some hypotheses concerning the comorbidity of MS and BD, and one hypothesis is that the disease itself may cause psychiatric manifestations, while another hypothesis suggests that both diseases have a common underlying pathophysiological process (33). Increased oxidative stress plays an important role in the pathogenesis of MS and leads to lipid peroxidation and inflammation (18). Similarly, previous studies have shown oxidative damage in the pathophysiology of BD (34), where some researchers indicated that the demyelinating lesions of MS patients occur in special areas of the brain that regulate the affective functioning, emotions, and pleasure involved in BD (35). Another hypothesis is a genetic relationship between MS and BD. It has been thought that there was a genetic link between MS and BD (36,37). Schiffer et al. (38) demonstrated that human leukocyte antigen genes were associated with both MS and BD.

Taking these into account, it is important to diagnose the co-occurrence of BP in MS patients, and clinicians should pay particular attention to treatment and to the effects on the quality of life in managing both

**Table 1.** Comparison of the TEMPS-A scores between the control and MS groups

TEMPS-A Scale	Control group (n=66)	MS patient group (n=65)	p
Depressive	6.83±5.08	8.97±4.38	0.01
Cyclothymic	5.65±5.27	8.48±4.84	0.002
Hyperthymic	8.12±4.98	7.92±4.80	0.817
Irritable	4.18±5.36	5.05±4.35	0.033
Anxious	5.67±6.30	8.42±5.81	0.002

TEMPS-A: Temperament Evaluation of Memphis, Pisa, Paris, and San Diego-Autoquestionnaire, MS: multiple sclerosis

**Table 2.** Comparison of MDQ and HCL-32 scores between the control and MS groups

Scales	Control group (n=66)	MS patient's group (n=65)	p
MDQ	5.79±3.53	5.11±2.77	0.243
HCL-32	14.64±6.43	14.03±6.81	0.651

MDQ: mood disorder questionnaire; HCL-32: 32-item hypomania checklist; MS: multiple sclerosis

**Table 3.** The relationship between disease type and the measures

Scales TEMPS-A	Relapsing remitting type MS	Secondary progressive type MS	p
Depressive	8.41±4.0	10.69±5.1	0.070
Cyclothymic	8.12±5.0	9.56±4.1	0.306
Hyperthymic	8.63±4.8	5.75±4.1	0.036
Irritable	4.71±4.1	6.06±4.9	0.430
Anxious	7.71±5.5	10.5±6.1	0.089
MDQ	5.57±2.7	3.69±2.3	0.017
HCL-32	14.6±6.7	12.1±6.9	0.282

TEMPS-A: temperament evaluation of Memphis, Pisa, Paris, and San Diego-autoquestionnaire; MDQ: mood disorder questionnaire; HCL-32: 32-item hypomania checklist; MS: multiple sclerosis

diseases. On the other hand, previous studies have suggested that MS patients have a higher lifetime prevalence of BD than the general population (33). Marrie et al. (39) analyzed 118 studies, and they found the prevalence of anxiety to be 21.9%, depression 23.7%, psychosis 4.3%, and BD 5.38% in MS patients. Another study also found a strong positive association between MS and BD and depression (40). Furthermore, Carta et al. (18) found that a lifetime prevalence of any mood disorder, DSM-IV bipolar, and major depressive disorders was higher in MS patients than in the controls. They confirmed the association between MS and BDs using the MDQ questionnaire and found higher MDQ scores in MS patients. Another study by Carta et al. (41) stated that patients with MS and comorbid BD had more impairment of the quality of life than the patients with MS without any BD diagnosis. In the present study, higher MDQ and TEMPS-A hyperthymic scores were found in MS patients for the relapsing remitting type versus the secondary progressive type. Previous studies reported a higher hyperthymic temperament in BD patients (42). Considering the episodic course of illness in BDs, rather than chronic progressive symptoms, and that temperament is a sub-clinical liability in mood disorders, it could be concluded that bipolarity might be specifically related to RRMS.

**Table 4.** The relation of TEMPS-A, HCI-32 and MDQ tests with general characteristics of the patient group

Scales	Disease Duration	EDSS scores
<b>TEMPS-A</b>		
Depressive	r=0.166	r=0.249
	p=0.187	p=0.046
Cyclothymic	r=-0.061	r=0.169
	p=0.631	p=0.177
Hyperthymic	r=-0.204	r=-0.312
	p=0.103	p=0.011
Irritable	r=0.060	r=-0.061
	p=0.635	p=0.632
Anxious	r=0.144	r=0.170
	p=0.253	p=0.175
HCI-32	r=-0.070	r=-0.208
	p=0.581	p=0.096
MDQ	r=-0.172	r=-0.244
	p=0.171	p=0.050

TEMPS-A: Temperament Evaluation of Memphis, Pisa, Paris, and San Diego-Autoquestionnaire; MDQ: mood disorder questionnaire; HCI-32: 32-item hypomania checklist; EDSS: expanded disability status scale

Depressive symptoms have been reported as a side-effect in MS patients who were on interferon beta treatment (43). In our study, an interesting point was that the patients who were on interferon beta I-b treatment had significantly higher MDQ scores than those taking interferon beta I-a or glatiramer acetate or who were without medication. These higher scores might not only indicate depression but also manic symptoms. Thus, a causal relationship between interferon beta I-b and mood symptoms needs to be clarified with further longitudinal studies.

Relapsing remitting MS characterized by episodic relapses and remissions is the most observed type of the disease. Approximately 10 years later, most RRMS patients develop SPMS, where the symptoms get worse without any remission (44). SPMS patients are more disabled, and EDSS scores tend to be higher than relapsing remitting ones (45). Previous studies stated that there was a positive correlation between EDSS scores and disease severity or progression (46). Tsigvoulis et al. (47) indicated that higher EDSS scores were strongly associated with depression and anxiety in MS patients. Recently, Askari et al. (48) reported that both MS patients with higher EDSS scores and those with SPMS had significantly higher BDI scores in their study. Consistent with these studies, we found statistically higher EDSS scores in SPMS patients than relapsing remitting ones; in addition, a positive correlation was determined between EDSS scores and TEMPS-A depressive and hyperthymic scores.

Many studies have reported that affective temperament subtypes were associated with mood disorders, and higher temperament scores might indicate a liability toward specific mood syndrome (49). Based on this evidence, the correlation of EDSS and hyperthymic-depressive temperament scores could be explained as an impact of the comorbidity of MS and mood disorder liability on disease severity.

There are some limitations of this study. First, our sample size was relatively small, and the study was of a cross-sectional design. Second, there was an absence of a psychiatric evaluation of the patients. Finally, the heterogeneity of the sample limits the generalizability of our findings.

In conclusion, our study is the first to evaluate both bipolarity and the affective temperament of MS patients. The high scores of affective temperaments, in which we found greater scores for RRMS patients with known subclinical manifestations of mood disorders, supports the high comorbidity rates of mood disorders in MS. The diagnosis and treatment of psychiatric disorders in MS patients are important because they affect the quality of life, prognosis, and also treatment adherence of MS patients. Thus, the screening of bipolarity and affective temperament profiles in MS patients could help clinicians predict future mood episodes and decrease their impact on disease severity.

**Ethics Committee Approval:** Authors declared that the research was conducted according to the principles of the World Medical Association Declaration of Helsinki "Ethical Principles for Medical Research Involving Human Subjects", (amended in October 2013).

**Informed Consent:** Written informed consent was obtained from patients who participated in this study.

**Peer-review:** Externally peer-reviewed.

**Author Contributions:** Concept – A.Ö., K.A.; Design – A.Ö., K.A.; Supervision – H.I.Ö.K.; Resources – A.Ö.; Materials – A.Ö.; Data Collection and/or Processing – A.Ö., K.A., E.R.K., H.M.Ş.; Analysis and/or Interpretation – A.Ö., K.A.; Literature Search – A.Ö., K.A.; Writing Manuscript – A.Ö., K.A.; Critical Review – A.Ö., K.A., H.I.Ö.K.; Other – A.Ö., K.A.

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