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Haematological and biochemical differences between mania and euthymia

Köse Çinar Rugül[a,*]
Görgülü Yasemin[a]
Sönmez Mehmet Bülent[a]
Kahyaci Kiliç Evnur[b]

[a] Assistant Professor, MD, Department of Psychiatry, Trakya University Faculty of Medicine, Edirne

[b] MD, Department of Psychiatry, Trakya University Faculty of Medicine, Edirne

TURKEY

ABSTRACT – *Background and Objectives:* The effects of transient hypothalamic dysfunction on the hypothalamic-pituitary-adrenal and hypothalamic-pituitary-thyroid axes can be shown by haematological and biochemical parameter changes. We hypothesized that manic episodes will be associated with subclinical inflammation, haemodilution and altered thyroid functions compared to euthymic states.

Methods: Patients admitted to the psychiatry clinic with manic episodes were identified. Those having comorbidities, except for thyroid dysfunctions, hypertension, hyperlipidemia, and type 2 diabetes mellitus, were excluded. Complete blood counts, total protein, albumin, and thyroid tests were recorded during the admissions (manic episodes) (Maletic, 2014 #24) and one year later (euthymic states) for the same patients.

Results: All studied parameters had significant differences between mania and euthymia. During manic episodes, patients had higher peripheral inflammatory indices (neutrophil/lymphocyte ratio and platelet/lymphocyte ratio), haemodilution (lower haemoglobin, haematocrit, total protein, and albumin), higher thyroxine and lower thyroid-stimulating hormone levels compared to euthymic states.

Conclusions: This study supports the hypothesis that compared to euthymic states; manic episodes are associated with low-grade inflammation, haemodilution and thyroid function abnormalities. Monitoring patients' blood compositions could result in better prognostic evaluations and aid in determining additional systemic treatment options, as well as in generating causal hypothesis to be tested in future studies.

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Introduction

Bipolar disorder (BD) can be counted among the diseases in which chronic cellular stress plays a role in the aetiology[1,2]. Inflammation contributes to the initiation and progression of several diseases that are aggravated by stress (e.g. dementia, cardiovascular and endocrinologic diseases, and some types of cancer)[3]. These diseases have high prevalences and earlier ages of and earlier ages of onset in patients with BD [4]. Stress impairs the normal regulation of leukocyte functions by the hypothalamic-pituitary-adrenal (HPA) axis and causes persistent low-grade inflammation[2,5]. The peripheral pathophysiology of BD appears to be related to systemic inflammatory mechanisms[3]. Moreover, inflammation has been proposed to be a causative factor for BD progression[6]. Persistent low-grade inflammation is more intense during mood episodes, especially manic episodes, and less intense in depressive episodes. Even euthymia has been associated with detectable peripheral inflammatory activity[4]. Cytokines, which are produced by immune cells and play important roles in cell signalling, lead to changes in lymphocyte, neutrophil and platelet levels[7]. There are only a few psychiatric disorder studies that have examined the neutrophil/lymphocyte ratio (NLR) and the platelet/lymphocyte ratio (PLR), both of which are considered inflammatory indices[8-12].

Between BD episodes, haematological and biochemical parameter differences were detected, even though the measures remained in the normal range[9]. This imbalance was explained by changes in fluid intake, physical activity levels or psychotropic drug use. Fluid and electrolyte redistribution within body compartments between different episodes was another explanation[9,13,14]. The latter explanation has been shown to be more realistic with a recent study showing a relative haemodilution in mania and haemoconcentration during depressive episodes[9].

The hypothalamus produces thyrotropin-releasing hormone, which stimulates the release of thyroid-stimulating hormone (TSH) from the anterior pituitary gland[15]. Stress has effects on the hypothalamic-pituitary-thyroid (HPT) axis[15,16]. HPT axis abnormalities are common in BD[17]. Thyroid patients present with higher rates of BD and hyperthyroidism may increase the risk of developing BD[18].

From a neurobiological perspective, pathological conditions showing similarities and differences produce a disease state that we call BD[19]. Current research emphasis is on the biological is on the biological markers that can be used in the diagnosis and can offer therapeutic options. Candidate peripheral biomarkers, like inflammatory and oxidative stress markers, neurotrophins and neurotransmitters, seem to change independently from the mood state[4,6,19,20]. We wanted to compare mania and euthymia in the same patients to see if the blood analyses differ between the two states.

Methods

Subjects

We reviewed electronic medical records of patients with BD diagnosed between January 2004 and December 2014. We identified and confirmed BD type I diagnoses via our inpatient and outpatient clinical records. All diagnoses were made according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR). Manic episode admissions with Young Mania Rating Scale scores greater than 20 were evaluated. Patients having data from both the manic episode and the euthymic state (ap-

proximately 1 year later) were selected. Patients having disease episodes within this 1-year period were excluded. From those patients with repeated admissions, the final admission was included in our data.

We excluded patients under 18 years of age. Patients having medical comorbidities, except for thyroid dysfunctions, hypertension, hyperlipidemia and type 2 diabetes mellitus, were also excluded. We further excluded patients having comorbid organic mental disorders or substance use disorders. This study was approved by the local ethics committee (TÜTF-BAEK 2015/61).

Measures

Patients' psychiatric evaluations and medical histories were recorded during their admissions and in their outpatient clinical examinations. Blood samples were collected between 8 to 10 a.m. and analyses were performed by the medical faculty's biochemical laboratories. NLR, PLR, haemoglobin (g/dL), haematocrit (%), total protein (g/dL), albumin (mg/dL), thyroxine (free T_4; ng/dL), and TSH (μIU/mL) levels were recorded. While NLR was calculated as the ratio between the absolute neutrophil and the absolute lymphocyte counts, PLR was calculated as the ratio between the absolute platelet and the absolute lymphocyte counts[10,21]. The total plasma protein level was used as a direct measure and haemoglobin, haematocrit and albumin levels were used as indirect measures of haemodilution/haemoconcentration[9].

We retrieved demographic and clinical data including sex, age in years at mania and euthymia, psychotic symptoms during the manic episode admission, and cigarette smoking. We also recorded the use of mood stabilizers and antipsychotic treatments at admission for the manic episode and during the euthymic state when blood samples were collected.

Statistical Analysis

We used SPSS version 20 (SPSS, Inc., Chicago, IL, USA) for statistical analysis. Descriptive statistics are expressed as mean ± standard deviation (SD) and rate (%). The Kolmogorov-Smirnov test was used to evaluate variable distributions. Haematological and biochemical parameters were compared between manic episodes and euthymic states in the same subjects. Student's *t*-tests (paired-samples *t*-tests) were performed on continuous variables with normal distributions, and Wilcoxon signed-ranks tests were used for continuous variables without normal distributions. Correlations were assessed by Pearson's or Spearman's correlation coefficients. The covariates included sex, age in years, cigarette smoking, psychotic symptoms during the manic episode admission, mood stabilizers and antipsychotic treatments. A p value of < 0.05 was considered statistically significant.

Results

In this retrospective study, we covered the data between 2004 and 2014. Data was gathered from an electronic database and our outpatient and inpatient clinical records. A total of 133 patients met the inclusion criteria. Their haematological and biochemical parameters from their most recent manic episodes and from their euthymic states (approximately 1 year after the manic episode) were analysed. The characteristics of the study population are presented in Table 1.

While all measurements were within the normal ranges, there were significant differences between mania and euthymia. During mania, NLR and PLR were higher than euthymia. However, mean haemoglobin, haematocrit, total protein and albumin levels

Table 1
Demographic and clinical characteristics of the study population (n = 133)

Characteristics	n (%) or mean ± SD
Gender, female, n (%)	67 (50.4)
Age at mania, mean ± SD	38.3 ± 11.2
Age at euthymia, mean ± SD	39.5 ± 11.7
Psychotic symptom presence (during mania), n (%)	87 (65.4)
Treatment during mania, n (%)	
Lithium	18 (13.5)
Valproate	21 (15.7)
Atypical antipsychotics	37 (27.8)
Typical antipsychotics	4 (3)
Treatment during euthymia, n (%)	
Lithium	65 (48.9)
Valproate	80 (60.2)
Atypical antipsychotics	98 (73.7)
Typical antipsychotics	11 (8.3)
Cigarette smoking, n (%)	75 (56.4)

were lower during mania. From the thyroid function tests, TSH was higher and free T4 was lower during manic episodes (Table 2).

During both mania and euthymia, haemoglobin and haematocrit levels were positively correlated with cigarette smoking (during mania for haemoglobin: rho = 0.184, $p = 0.04$ and for haematocrit: rho = 0.191, $p = 0.033$; during euthymia for haemoglobin: rho = 0.272, $p = 0.002$ and for haematocrit: rho = 0.324, $p = 0.000$). The euthymia NLR was negatively correlated with lithium use (rho = -0.272, $p = 0.002$) and positively correlated with valproate use (rho = 0.202, $p = 0.022$). Also, euthymia PLR was negatively correlated with lithium use (rho = -0.246, $p = 0.005$) and positively associated with valproate use (rho = 0.221, $p = 0.012$).

Discussion

The present study revealed that bipolar patients experiencing mania had higher peripheral inflammatory indices, like NLR and PLR, while having lower haemoglobin, haematocrit, total protein and albumin levels. Patients experiencing mania also had higher thyroxine levels, and lower TSH levels compared to euthymia. These results indicate that patients with a diagnosis of bipolar I disorder during manic episodes have immune system activation, haemodilution, and thyroid function abnormalities[3,9,18]. All of these changes may result from transient hypothalamic dysfunction.BD fits into the stress model[4,22]. In the stress model, there is a cascade of changes beginning with glucocorticoid receptor

Table 2
Manic episode and euthymic state hematologic and biochemical parameter measurements (mean ± standard deviation) of the study population (n = 133)

Measurements	Patients, n	Mania	Euthymia	p-value
NLR	120	2.4 ± 1.7	1.9 ± 0.6	< 0.005[b]
PLR	120	121.1 ± 54.7	108.7 ± 37.1	0.01[b]
Hemoglobin (g/dL)	120	13.3 ± 1.3	13.9 ± 1.3	< 0.005[a]
Hematocrit (%)	120	40.2 ± 3.5	41.8 ± 5.9	< 0.005[b]
Total protein (g/dL)	46	6.8 ± 0.6	7.3 ± 0.5	< 0.005[a]
Albumin (mg/dL)	45	4.1 ± 0.4	4.4 ± 0.3	< 0.005[a]
Free T_4 (ng/dL)	77	1.1 ± 0.2	1.0 ± 0.1	0.009[a]
TSH (mIU/mL)	80	1.9 ± 1.4	2.3 ± 1.7	0.007[b]

[a] Paired Samples *t*-test.

[b] Wilcoxon Signed Ranks test.

insufficiency and increases in cortisol levels[4,22]. HPA axis dysregulation, which includes reduced sensitivity to glucocorticoids, causes the inflammatory activation[2,19]. Inflammation is also increased in the periphery of the body in both depressive and manic episodes and returns to subnormal levels during the euthymic state[23].

NLR and PLR have been proposed as markers of inflammation in distinct populations and have prognostic and predictive values[24]. They have been associated with poor prognoses and are considered independent predictors of mortality in various diseases and cancers[24-26]. NLR can be calculated based on a complete blood count and is superior to other leucocyte parameters (e.g. neutrophil, lymphocyte and total leucocyte counts) because its stability is less influenced by physiological, pathological and physical factors[27]. Schizophrenia patients were found to have higher NLRs compared to healthy controls[8,11]. In a study comparing drug naive manic and schizophrenic patients, mania was associated with increased leucocyte and neutrophil levels compared to schizophrenia[28]. As far as we know, there is only one study comparing NLR and PLR ratios in BD and controls. In this study, NLR and PLR were higher in both manic and euthymic patients compared to the controls[12]. Our findings support the inflammatory nature of mania. In our sample, both NLR and PLR were significantly increased in mania compared to euthymia. Due to our correlation analyses, NLR and PLR were negatively associated with lithium use and positively associated with valproate use at euthymia. Mood stabilizers, such as lithium, have been hypothesized to regulate the transcription and gene expression of factors critically involved in anti-inflammatory effects[29].

Comorbid diseases and BD seem to share similar underlying pathophysiologic mechanisms[3,30]. Systemic inflammation shown by elevated leucocyte counts during mania was among the risk factors for early natural death of BD[31]. The leading cause of excess death in BD patients has not been due to the bipolar symptomatology, but rather, vascular diseases (e.g. myocardial infarction, stroke)[32]. Psychotropic drug use is still a risk factor for the development of systemic comorbidities,

but psychotropic drug use has also been postulated to be a factor in protecting against early natural death[31,33].

Both acute and chronic stress have been shown to cause haemoconcentration. This phenomenon is called "stress-haemoconcentration" and is caused by altered catecholaminergic homeostasis and blood pressure[14,34,35]. While major depression and bipolar depression have been associated with stress-haemoconcentration, mania has been associated with haemodilution[9,13,14].

Hochman and colleagues evaluated 175 manic and depressive hospital admissions of 43 bipolar patients. They concluded that there was a significant reduction in haemoglobin, haematocrit and albumin levels in mania patients compared to those with depression, indicating that mania may be associated with a relative haemodilution and depression with haemoconcentration[9]. The same group compared psychosis, mania and depression and found that manic patients had lower total protein and higher leucocyte counts[13]. Transient hypothalamic dysfunction is a postulated underlying mechanism[36,37]. Cigarette smoking, bad dietary habits, low physical activity levels, and psychotropic drug use increase the risk of comorbid diseases and may cause haematological and biochemical irregularities[38,39].

In the present study, cigarette smoking was positively related to haemoglobin and haematocrit levels. A recent population study found an association between low-grade inflammation and lower haemoglobin levels in healthy individuals based on the assumption that chronic inflammation leads to chronic disease anaemia due to the sequestration of iron caused by inflammatory cytokines[40]. This same group found a positive correlation between cigarette smoking and increased inflammation and haemoglobin levels[40]. Due to carbon monoxide exposure, cigarette smokers show increased levels of inflammation[41].

In our study, during manic episodes, patients had higher free T4 and lower TSH levels compared to their euthymic states. Thyroid dysfunction has been associated with BD[42]. Besides affecting immune function, elevated glucocorticoids have been associated with suppression of TSH secretion[43]. Also, increased dopaminergic activity during mania, especially with psychotic features, affects pituitary secretory functions and may lead to reduced TSH levels[44]. Nearly half of our patients during euthymia were taking lithium and lithium-exposed patients show higher rates of hypothyroidism[45]. This is another reason for the relative increase of free T4 and decrease of TSH during mania. Furthermore, during euthymia, antipsychotic use was higher than during mania, and antipsychotics have been shown to affect serum thyroid hormone levels[46]. In addition to higher level dysfunctions, thyroid hormone receptors or transporters are held responsible for the brain's hypo- or hyperthyroidism, which occurs in systemic euthyroidism[47].

A recent study comparing TSH levels between schizophrenia, unipolar depression, and BD reported that patients with bipolar mania had the lowest level of TSH while the highest level was found in patients with bipolar depression[16]. Subclinical hypothyroidism was found to be present in drug-naive schizophrenic patients and treatment with antipsychotics increased basal TSH levels[48]. Transient euthyroid hyperthyroxinaemia has been commonly noted in acutely admitted psychiatric patients, including those with depression. Such elevations are thought to be a result of the stress of hospitalization[49].

A limitation of our study is its retrospective design. Patients were evaluated during their manic episode hospital admissions and during their euthymic states approximately one year later. We did not want residual symptoms to have effects on the results, thus, a 1-year time

interval was determined according to the treatment guidelines[50]. We evaluated the changes within the same patients with the proper time interval, and this is the strength of the study. Another limitation of the study is the exclusion of data about drugs other than psychotropic drugs. We also did not have data concerning body mass indices of the patients, whether they were performing exercise or on a diet, and if there was any form of substance use prior to the blood analyses.

In conclusion, our results indicate that mania is associated with low-grade inflammation, haemodilution and thyroid function abnormalities compared to euthymia. Changes in the studied parameters can be explained by HPA axis and autonomic dysregulation. We assume that these parameters, taken together, may be used as state markers as well as treatment response markers. Larger, prospective studies including depressive episodes will be useful to clarify this.

Contributors

All authors contributed to the design of the experiment, acquisition and analysis of data, and preparation of the manuscript. All authors have approved the final version of the manuscript submitted.

Conflict of interest and disclosure

The authors declare no conflict of interest.

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* Corresponding author:
Rugül KÖSE ÇINAR
Assistant Professor, MD
Department of Psychiatry
Trakya University Faculty of Medicine
Edirne, Turkey
Tel: 905 337 330407
Fax: 902 842 353451
E-mail: rugulkose@hotmail.com