Levels of basophils and eosinophils are elevated while lymphocytes are reduced in patients with panic disorder compared to controls: a preliminary study

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ABSTRACT

OBJECTIVE: This study evaluates total blood count especially white blood cells (WBCs) in patients with panic disorder, based on the possible association between the immunologic system and panic disorder.

METHODS: Whole total blood count parameters were detected by using an auto-analyser in 40 patients with panic disorder and the same number of healthy comparison subjects. To detect the severity of panic disorder and depression, the Hamilton Depression Rating Scale and the Panic Agoraphobia Scales were used.

RESULTS: Patients with panic disorder and healthy subjects were not different in regard to red blood cell count and related haematological parameters including haemoglobin, haematocrit, mean corpuscular volume, mean corpuscular haemoglobin, and mean corpuscular haemoglobin concentration and platelet count. As for the WBC parameters, total WBC, neutrophil, and monocyte counts of the patients with panic disorder were similar those of healthy comparisons. However, basophil (0.02 ± 0.02/mm 3 for the control subjects versus 0.05 ± 0.05/mm 3 for the patient group), eosinophil (0.18 ± 0.13/mm 3 for the control subjects versus 0.37 ± 0.24/mm 3 for the patient group), and lymphocyte (2.50 ± 0.69/mm 3 for the control subjects versus 2.06 ± 0.80/mm 3 for the patient group) counts were statistically significantly different in the patient group compared to healthy subjects.

CONCLUSION: In summary, this study represents the first published report of total haematological parameters in patients with panic disorder. Though further replication is required to confirm this association, there seems to be a relationship between panic disorder and immunologic system.

ABBREVIATIONS: DSM-IV: Diagnostic and Statistical Manual of Mental Disorders, 4th ed.; HCT: haematocrit; HDRS: Hamilton Depression Rating Scale; HGB: haemoglobin; HLA: human leukocyte antigen; IFN-γ: Interferon; IL-4: Interleukin-4; MCH: mean corpuscular haemoglobin; MCHC: mean corpuscular haemoglobin concentration; MCV: mean corpuscular volume; NK: natural killer cell; OCD: obsessive compulsive disorder; PAS: Panic Agoraphobia Scales; PD: panic disorder; RBC: red blood cell count; TNF: tumour necrotising factor; WBC: white blood cell

Introduction

Panic disorder is chronic and often disabling anxiety disorder. It is characterized by unexpected panic attacks. Panic disorder is one of the anxiety disorder, classified in the Diagnostic and Statistical Manual of Mental Disorders, 5th ed. (DSM-5), and is characterized by unexpected paroxysms of severe panic attacks related to catastrophic cognitions which include “I will die” or “I am suffering a heart attack.” It leads to considerable impairment in the patients’ occupational, familial, and social life. Panic attacks consist of a variety of physiological symptoms such as palpitation, sweating, shaking, or arterial tension changes beyond cognitive errors mentioned above.

As in other psychiatric disorders, panic disorder has also multifactorial etiopathogenetic factors from animal models to neuroimaging investigations. In literature, it has been some studies indicating that haematological parameters can be used as biomarkers in a variety of psychiatric disorders [1–4]. It should be noted that panic disorder is one that etiopathogenesis has been well accounted for compared to other anxiety disorders. Contemporary knowledge reveals that panic disorder occurs a variety of neurobiological roots including abnormalities in neurohormones and neurotransmitters, autonomous system dysfunction, disablement in a variety of receptor system function, and neuroimaging alterations both structurally and functionally.
functionally. Apart from these, another area which may be associated with the etiopathogenesis is immunological factors. We think that because of their multifactorial nature, haematological parameters can be used as biomarkers in some psychiatric disorders such as OCD and panic disorder since this method is cheap, practical, and effective. This type of use of haematological parameters can provide some beneficial for diagnosis and treatment [5–9]. First efforts start with the notion that the patients with panic disorder may have a hypersensitive alarm system which causes to a pathologic exaggerated reaction to physiologic signs of potential suffocation which can affect patients’ haematological parameters [10]. In this context, Ross et al. [11] examined haematological indices in the patient with panic disorder patients and healthy controls, with the hypothesis that hypersensitive suffocation alarm system aforementioned might erroneously affect haematological changes, maladaptive to the real environment, and found that MCH might be relatively increased. On the other hand, the panic disorder itself is reported to be related to a high frequency of comorbid immunological diseases such as type I allergy and obstructive lung disorders like asthma [12,13]. Thing that all these investigations aforementioned revealed is that there may be an existence of a possible immune dysfunction in panic disorder. Previously, in association with this, the growing evidence implicates that the immunologic factors may be associated with the pathophysiology of some subtypes of OCD, we examined total blood count in thirty patients and same number of healthy controls and found that there were no significant differences between the groups regarding any haematological parameter except for neutrophil count whereas the mean neutrophil count of the patient group was lower compared to that of the control subjects [14]. Consequently, we suggested that our findings might contribute to the role of immunological factors in the pathogenesis of OCD. In comorbidity studies, it was revealed that a relationship between panic disorder and OCD, but little is known about the real relationship. Rasmussen and Eisen reported a much higher frequency of panic attacks and panic disorder than that estimated in the general population, with the rate of 60% of panic attacks and that of 15% of 200 cases with the comorbid panic disorder in OCD patients throughout their life [15].

On the one hand, immunological data on panic disorder mentioned above, on the other hand, in association with the panic disorder’s intense OCD comorbidity, led us to evaluate total blood count especially WBCs in the patients with panic disorder.

**Methods**

All patients (n = 40), with the mean age of 31.55 ± 5.80 years, had a DSM-IV edition of panic disorder and were followed by Firat University School of Medicine Department of Psychiatry in-patient or out-patient clinics. The patients were those who applied to our unit within the last one year and were either drug naïve or taking stable drug dosages at least last two months, with the following exclusion criteria: Existence of any Axis I comorbidity including depressive disorder, use of anti-inflammatory agents or clinically relevant abnormal laboratory tests including any anemia, the history of any endocrinologic condition, females who are pregnant or lactating, serious and unstable medical illnesses, substance dependence within the previous 3 months, the existence of medical conditions which might affect changes in metabolic parameters, the history of diabetes or lipid disorder, or use of anti-diabetic or lipid-lowering therapy or special diets to affect haematological parameters. Their hospital files were screened and accessed to their information. Healthy control subjects (n = 40) were selected among the individuals’ files who had no current or lifetime history on their own or first-degree relatives of any psychiatric disorders. Comparison subjects were matched with the patients in regard to sex and age. Also, they should not have had any endocrinologic state, clinically relevant abnormal laboratory tests including any anemia, use of anti-inflammatory agents, being pregnant or lactating, the existence of medical conditions which might affect changes in metabolic parameters, serious and unstable medical illnesses, substance dependence within the previous 3 months, the history of diabetes or lipid disorder, or use of anti-diabetic or lipid-lowering therapy or special diets to affect haematological parameters. In fact, at baseline, considering that they were available to include into the study, 57 patients with panic disorder and 53 healthy controls were screened. But 17 patients and 28 healthy controls were excluded from the study. For the patient group, 11 had comorbid diagnoses, 4 had anemia, and 2 had medical diseases. For the control group, eight had a family history, four had anemia, and one had a medical disease. Local Ethics Committee approval was obtained, with the date of 16th February 2016 and number of 04/04. For detecting the severity of panic disorder and depression, the HDRS and the PAS were used [16,17]. For both scales, reliability and validity studies were done [18,19].

The procedure of sample collection and measure of haematological parameters

Heparinized venous blood samples had been obtained from forearm vein of the subjects, as routinely in our hospital. For each subject, between 7 and 8 am after overnight fasting, they had been collected into 5 ml vacutainer tubes containing potassium EDTA. All total blood count parameters were detected by using
an auto-analyser (Coulter Max M, Coulter Electronics Ltd, Luton, U.K.).

**Statistical evaluation**

We performed all statistical analyses using the SPSS for Windows software, version 13.0 (SPSS, Chicago, IL). Alpha was set at \( p < .05 \). Correlation analyses were done by using Spearman’s rank test. To compare the demographic, clinical, and haematological variables between the panic disordered patients and the healthy control subjects, independent \( t \)-test was used. Demographics, clinical measures, and laboratory values were reported using descriptive statistics. Evaluations were two-tailed. For the independent samples \( t \)-test, Cohen’s \( d \) was determined.

**Results**

In Table 1, it is demonstrated the clinical features, demographic, and haematological parameters of the panic disorder and healthy comparison subjects. With regard to gender ratio (female/male) (patients 25/15, controls 26/14), age (patients 31.55 ± 5.80, controls 30.80 ± 4.66), educational level, or smoking status, no difference was found between the patients with panic disorder and healthy subjects \((p > .05)\). As for the scale scores, the mean HDRS scores of the patients were significantly higher than healthy comparison subjects, with the scores of 12.08 ± 4.12 and 6.83 ± 2.49, respectively \((t = 6.90, p < .001)\). The average PAS score in the patient group was 15.63 ± 4.71 (Table 1).

Patients with panic disorder and healthy subjects were not different in regard to RBC and related haematological parameters including HGB, HCT, MCV, MCH, and MCHC, as can be seen in Table 1.

In addition, platelet counts did not differ between the groups. As for the WBC parameters, total WBC, neutrophil, and monocyte counts of the patients with panic disorder were similar to those of healthy comparisons. However, basophil \((0.02 ± 0.02/mm^3)\) for the control subjects \(versus 0.05 ± 0.05/mm^3\) for the patient group), eosinophil \((0.18 ± 0.13/mm^3)\) for the control subjects \(versus 0.37 ± 0.24/mm^3\) for the patient group), and lymphocyte \((2.50 ± 0.69/mm^3)\) for the control subjects \(versus 2.06 ± 0.80/mm^3\) for the patient group) counts were statistically significantly different in the patient group compared to healthy subjects, using independent \( t \)-test \((t = 3.00, p < .001)\ for basophil count; \(t = -4.33, p < .001\) for eosinophil count; and \(t = 2.65, p < .01\) for lymphocyte count). Cohen’s \( d \) values were 0.59, with \( r \)-value of 0.28 for lymphocyte count, 0.79, with \( r \)-value of 0.37 for basophil count, and 0.98, with \( r \)-value of 0.44 for eosinophil count. Using Spearman’s rank correlation test, no correlational relationships were determined between PAS, or HDRS scores and any haematological parameters measured in the patient group \((p > .05)\).

**Discussion**

The principal findings of the present study were statistically significantly different basophil, eosinophil, and lymphocyte count in the patient group compared to healthy subjects, using independent \( t \)-test, while no differences were detected in regard to other WBC parameters and other haematological parameters. With regard to the alteration of the haematological parameters in panic disorder, first efforts began with the thought that the patients with panic disorder may have a hypersensitive alarm system which cause to a pathologic exaggerated reaction to physiologic signs of potential suffocation which can affect patients’ haematological parameters [10]. Ross et al. examined haematological indices in patients with panic disorder and healthy controls, with the hypothesis that hypersensitive suffocation alarm system aforementioned might erroneously affect haematological changes, maladaptive to the real environment [11]. Resembling the subjects with chronic obstructive pulmonary disease or high-altitude dwellers, they found that MCH might be relatively increased. In another study, Balon et al. did not detect any significant differences on MCV, MCH, and MCHC between the patients with panic disorder and healthy controls, with the hypothesis that hypersensitive suffocation alarm system aforementioned might erroneously affect haematological changes, maladaptive to the real environment. Thus, at least in partial, our results were not accordance with the investigations mentioned above. First of all, the pure nature of our patient group which did not include any comorbidity including agoraphobia apart from depression beyond detailed exclusion criteria to

| Table 1. Demographic and haematological parameters. |
|---------|------------|------------|--------------|-------|
| **Patients** \((n = 40)\) | **Controls** \((n = 40)\) | \( t \) | \( p \) |
| **Age** | 31.55 ± 5.80 | 30.80 ± 4.66 | 0.64 | .53 |
| **Gender (F/M)** | 25/15 | 26/14 | - | - |
| **PAS** | 15.63 ± 4.71 | - | - | - |
| **WBC** | 7.47 ± 1.66 | 7.70 ± 2.02 | -0.56 | .58 |
| **Neutrophil** | 4.21 ± 1.35 | 4.63 ± 1.62 | -1.25 | .22 |
| **Lymphocyte** | 2.50 ± 0.69 | 2.06 ± 0.80 | 2.65 | .01 |
| **Eosinophil** | 0.18 ± 0.13 | 0.37 ± 0.24 | -4.33 | .00 |
| **Basophil** | 0.05 ± 0.05 | 0.02 ± 0.02 | 3.00 | .00 |
| **Monocyte** | 0.46 ± 0.21 | 0.52 ± 0.15 | -1.64 | .10 |
| **Platelet** | 251.30 ± 64.32 | 271.90 ± 75.86 | -1.31 | .19 |
| **Red blood cells** | 4.79 ± 0.31 | 4.83 ± 0.44 | -0.51 | .61 |
| **HGB** | 13.90 ± 1.83 | 13.60 ± 1.42 | 0.80 | .43 |
| **HCT** | 41.26 ± 5.45 | 40.57 ± 4.51 | 0.62 | .54 |
| **MCV** | 84.38 ± 13.94 | 84.93 ± 6.39 | -0.23 | .82 |
| **MCH** | 29.07 ± 2.36 | 28.77 ± 2.63 | 0.53 | .60 |
| **MCHC** | 33.76 ± 1.55 | 33.88 ± 2.19 | -0.27 | .79 |
| **HDRS** | 12.08 ± 4.12 | 6.83 ± 2.49 | 6.90 | .00 |
rule out organic factors may account for these differences. As for the second part of the investigation, that is, WBC and related parameters, some important findings were obtained. Some investigations emphasized the strong relationship between panic disorder and comorbid immunological diseases such as type I allergy and obstructive lung disorders like asthma. In their investigation, Jasnoski et al. found a high incidence of panic attacks in the patients with a history of type I allergies [12]. Another support came from Kennedy et al. and Schmidt-Traub and Bamler who reported that type I allergy frequency in the patients with panic disorder was up to 70% [22,23]. On the other hand, Kim et al. evaluated 26 panic disordered patients who were treated with paroxetine for three months and the same number of healthy controls and measured the lymphocyte subsets, psychopathological characteristics and serum catecholamine values [24]. They found that the patients with panic disorder showed increased CD3+, CD4+, and CD8+ T lymphocyte proportions and a decreased B lymphocyte proportion by using three of paroxetine treatment and concluded that pharmacological treatment with a pharmacological agent might affect immune function in these patients. Schleifer et al. [25] reported no difference in T cell, B cell, T helper, T suppressor and NK cell numbers for uncomplicated panic disorder patients whereas Marazziti et al. determined that the patients with panic disorder had reduced numbers of helper T cells compared with both depressed patients and normal volunteers [26]. Rapp et al. demonstrated that panic patients with no other current major psychiatric disorders showed increased numbers of B lymphocytes, NK cells, and HLA-DR-presenting cells compared with both patients with social phobia and control subjects [13]. Haematological parameters are affected by a variety of intrinsic and extrinsic factors. In this study, as much we excluded a major part of these factors such as anemia and use of anti-inflammatory agents, it is not possible to exclude everything. Consequently, we consider that our present findings revealing that the basophil, eosinophil, and lymphocyte values of the patients were significantly lower when compared to those of healthy subjects support the relationship between panic disorder and comorbid immunological and allergic diseases. On the other hand, we are in accordance with the Ross et al.’s comments indicating that hypersensitive suffocation alarm system aforementioned might erroneously affect haematological changes, maladaptive to the real environment [11]. It has been reported that glucocorticoid levels, especially in patients who withdrew from steroid treatment, are closely related to depression, suicidal behavior, and panic disorder [27]. In addition, glucocorticoids could lead to reduced counts of eosinophil and basophil by apoptosis [28]. In the present paper, we could not account for increased eosinophil and basophil, so we need future studies with larger sample.

Our present investigation has some limitations. One of them is, of course, its small sample size. Second one is that we did not include other cytokines and pro-inflammatory markers, such as TNF-α, IL-4, IL-6, IL-10, and IFN-γ in whole blood cultures, and NK cell activity and peripheral blood NK cell, T cell, and B cell counts.

In summary, this study represents the first published report of total haematological parameters in the patients with panic disorder. Though further replication is required to confirm this association, there seems to be a relationship between panic disorder and immunologic system.

Disclosure statement

No potential conflict of interest was reported by the authors.

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