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Original research article

A study of chemokines, chemokine receptors and interleukin-6 in patients with panic disorder, personality disorders and their co-morbidity

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ABSTRACT

Background: Stress may induce inflammatory changes in the immune system and activate pro-inflammatory cytokines and their receptors by activating the hypothalamic–pituitary–adrenal axis.
Methods: 460 hospitalized patients with panic disorders (PD) and/or personality disorders (P) were studied. The study group comprised subjects with PD, avoidant personality disorder (APD), borderline personality disorder (BPD), obsessive-compulsive personality disorder (OCPD), and concomitant (PD + APD; PD + BPD; PD + OCPD). Each study group consisted of 60 subjects (30 females and 30 males). The control group included 20 females and 20 males without any history of mental disorder. ELISA was used to assess the levels of chemokines: CCL-5/RANTES (regulated on activation, normal T-cell expressed and secreted), CXCL-12/SDF-1 (stromal derived factor), their receptors CXCR-5 (C-C chemokine receptor type-5), CXCR-4 (chemokine C-X-C motif receptor-4), and IL-6.
Results: Statistically significant differences in the levels of CCL-5 and CCR-5 were revealed between all study groups. The greatest differences were found between the groups with PD + OCPD and PD + APD. Moreover, concomitance of PD with P significantly increased the level of chemokines and their receptors in all study groups *versus* the subjects with P alone.
Conclusions: The results of the study show differences between the groups. To be specific, inflammatory markers were more elevated in the study groups than the controls. Therefore, chemokines and chemokine receptors may be used as inflammatory markers in patients with PD co-existent with P to indicate disease severity. PD was found to be a factor in maintaining inflammatory activity in the immune system in patients with P.

Introduction

Personality disorders are characterized by enduring maladaptive behavioral patterns that affect proper human functioning. They are most frequently manifested in such areas as affect dysregulation, control of impulsive behaviors, style of reasoning, experiencing of emotions, and also in maintaining relations with others. Anxiety is one of the major symptoms observed in personality disorders, particularly in avoidant personality disorder (APD), borderline personality disorder (BPD) and obsessive-compulsive personality disorder (OCPD). Anxiety may give rise to the development of various anxiety disorders, including panic disorder (PD). Moreover, primarily occurring panic disorders may predispose individuals toward developing personality disorders later in their lives. Panic attacks usually occur suddenly and result from catastrophic thinking rather than being a real danger to the patient [1].

Cytokines participating in the neuroimmunological processes associated with anxiety are, amongst others, the chemokine CCL-5/RANTES (regulated on activation, normal T-cell expressed and secreted), and its receptor CCR-5 (C-C chemokine receptor type-5), the chemokine CXCL-12/SDF-1 (stromal derived factor), and its receptor CXCR-4 (chemokine C-X-C motif receptor-4), as well as interleukin-6 (IL-6) [2].

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The RANTES chemokine is the first significant chemokine involved in inflammation that effects T lymphocytes to increase the expression of the receptors for interleukin-2 (IL-2). Additionally, it participates in the processes of neurodegeneration and neuroprotection. Brenneman et al. [3] revealed that the RANTES chemokine exerts a neuroprotective influence on *in vitro* neuronal cultures in which the presence of the glycoprotein GP120 (GP120) induced neurodegeneration. Other studies have revealed that injection of the neurotoxic factor N-methyl-D-aspartate (NMDA) into the hippocampus of rats caused an increase in the expression of the CCL-5 receptors [4].

SDF-1 constitutes another significant chemokine concerning the immune response. It is secreted by the central nervous system, especially expressed on the surface of astrocytes. Following the observation of Liu et al. [5], CXCL-12 has been found to have a neurodegenerative effect. On the contrary, an analysis of the astrocytic cultures incubated with CXCL-12 revealed an increase in the secretion of the basic fibroblast growth factor (bFGF), which acts neurotrophically. Bezii et al. [6] showed that CXCL-12 and CXCR-4 are involved in the communication between microglial cells/astrocytes and neurons. Hoge et al. [7] demonstrated an increased level of the following cytokines: IL-6, interleukin-1α (IL-1α), interleukin-8 (IL-8), monocyte chemoattractant protein-1 (MCP-1), C-C motif chemokine-11 (eotaxin/CCL-11), and interferon-α (IFN-α), in patients with PD alone.

IL-6 was one of the first cytokines reported to participate in the neuroimmunological inflammatory process. It stimulates T lymphocytes and induces the synthesis of glucocorticosteroids in the central nervous system. The literature confirms the role of IL-6 in mental disorders and neuroinfectious diseases [2,7]. Sutin et al. [8] revealed an increased level of IL-6 in patients with high level of neuroticism. In another study by Kahl et al. [9], the authors noticed an increased level of cortisol, tumor necrosis factor-α (TNF-α), IL-6, and cortisol to dehydroepiandrosterone (DHEA) in patients with depression concomitant with BPD.

The previously conducted studies on determining the concentrations of pro-inflammatory cytokines and their receptors involved patients with either generalized anxiety disorders (GAD) or post-traumatic stress disorder (PTSD). In a study by Oglodek et al. [10], the authors revealed an increase in the concentrations of the chemokines CCL-5 and CXCL-12, as well as the receptors CCR-5 and CXCR-4 in patients with PTSD and APD. The concentrations of the chemokines CCL-5 and CXCL-12, as well as the receptors CCR-5 and CXCR-4 were higher in females than in males. Guo et al. [11] found an increase in the levels of such cytokines as IL-2, interleukin-4 (IL-4), IL-6, IL-8, intrleukin-10 (IL-10) in patients with PTSD, yet without concomitant personality disorders. In another study by Oglodek et al. [12], the authors revealed elevated concentrations of the chemokines SDF-1, CCL-5 and SDF-1 in patients with comorbid GAD+APD, GAD+BPD and GAD+OCPD. In addition, Diaz-Marsá et al. [13] and Kahl et al. [14] observed an increase in the serum concentrations of interleukin-1β (IL-1β), TNF-α and IL-6 in patients with BPD and concurrent depression. In a study by Vogelzangs et al. [15], subjects with GAD, social phobia, PD or agoraphobia were also found to have elevated concentrations of the above interleukins and C-reactive protein (CRP).

Existing studies which have investigated the participation of chemokines in anxiety disorders and personality disorders failed to concentrate on the comparison of patient groups suffering from both panic disorder and personality disorder. Furthermore, they failed to compare the differences in the concentrations of chemokines in males and females with various personality disorders. Therefore, conducting these studies appears to be significant for future diagnosis and treatment of patients with both PD and personality disorder.

The aim of the study was to compare the concentration levels of chemokines in patients diagnosed with either personality disorder or PD with the concentration levels of the same chemokines in subjects suffering from both types of disorder.

An analysis of changes in the concentrations of chemokines between these patient groups may serve as an indicator of the level of disturbance to the immune balance responsible for the development of mental illnesses.

Materials and method

Participants

The study involved 460 participants. The study group comprised 420 subjects (210 males and 210 females) at the age of 42.4 ± 5.2 (25–48 years old). The study group involved patients with personality disorders (groups of 60 subjects with avoidant, borderline and obsessive-compulsive personality), patients with personality disorders co-existent with panic disorders (groups of 60 patients with avoidant, borderline and obsessive-compulsive personality), as well as 60 patients with PD. Each group of 60 subjects comprised 30 females and 30 males.

The diagnosis of personality disorder and PD in patients who were enrolled in 2012 and in the first half of 2013 (311 patients in total) was performed by means of the Diagnostic and Statistical Manual of Mental Disorders-IV (DSM-IV) criteria. However, for patients who were enrolled between the second half of 2013 and the first half of 2015 (109 patients in total), the DSM-V criteria were used. Patients comprising the study group underwent treatment for mental illness at the Department of Psychiatry of the Collegium Medicum in Bydgoszcz between 2012 and 2015. The patients diagnosed with personality disorder alone were hospitalized in order to undergo psychotherapy. However, they did not receive any medication.

The control group involved 40 healthy subjects (20 females and 20 males) assigned according to sex and age. The average age in the control group was 42.4 ± 4.1 (25–48 years old). The following exclusion criteria were used for both groups in the study: diagnosis of mental illnesses not indicated, organic damage to the central nervous system, detected alcohol or other psychoactive substance abuse, treatment of infectious and chronic systemic diseases. The exclusion criteria also applied to individuals with smoking habits and taking medication. Moreover, the study and control groups comprised only non-menopausal females who had had their blood collected in their follicular phase of the menstrual cycle. All the study participants had fasting blood samples of 15 ml collected from the median cubital vein.

Method to determine chemokine concentrations

All patients had blood samples collected between 7:00 and 9:00 a.m. The blood samples were then centrifuged at 3500 rpm for 10 min. Following centrifugation, the plasma samples were pipetted into sterile 2 ml microcentrifuge tubes and stored at −70 °C until laboratory analysis. Concentrations of chemokines and their receptors were determined by ELISA and they included: CCL-2/MCP-1 (Diaclone, France), CCL-5/RANTES (USCN), CXCR-5 (USCN), SDF-1 (USCN), CXCR-4 (USCN), and IL-6 (kit from Diaclone, France). Chemokines and their receptors were determined in duplicate in appropriately diluted plasma samples. Standard solutions were put onto the plate to verify reliability of the results. Concentrations were measured and a calibration curve was prepared. Then, the plasma samples were applied and a color reaction was produced. Color intensity corresponded to the concentration levels of chemokines and their receptors in the samples. The detection levels of cytokines and their receptors