Original Article
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Transdiagnostic Associations between Anger Hostility and Chemokine Interferon-gamma Inducible Protein 10

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Objective: Many psychiatric disorders are linked to low grade systemic inflammation as measured by systemic cytokine levels. Exploration of cytokines and immune activity and their role in psychiatric symptoms may inform pathobiology and treatment opportunities. The aim of this study is to explore if there are associations between cytokines and psychiatric symptom clusters. Comparison between patients regularly using and those not using psychotropic medication is also conducted.
Methods: This was a cross sectional naturalistic study with 132 participants from a general open inpatient psychiatric ward at the Nordland Hospital Trust, Norway. Serum levels of 28 different cytokines were assessed. Psychiatric symptoms the last week were assessed by a self-rating scale (Symptom check list, SCL-90-R) and grouped in defined clusters. Multiple linear regression model was used for statistical analyses of associations between levels of cytokines and symptoms, adjusting for possible confounding factors.
Results: We found a positive association (p = 0.009) between the chemokine interferon-gamma inducible protein 10 (CXCL 10; IP-10) and the anger hostility cluster. No associations were found between the other symptom clusters and cytokines. IP-10 and the anger hostility cluster were positively associated (p = 0.002) in the subgroup of patients using psychotropic medication, not in the subgroup not using psychotropic medication.
Conclusion: Our analyses revealed a significant positive association between the symptom cluster anger hostility in SCL-90-R and the chemokine IP-10 in the subgroup of patients using psychotropic medications.

KEY WORDS: Immune system; Cytokines; Psychiatry; Neuroscience.

INTRODUCTION

Altered immune activity is seen in several psychiatric disorders. A potential causative effect of inflammation on psychiatric symptoms, as well as the other way around, cannot be ruled out. This may have implications for prevention and treatment of psychiatric disorders. Inflammatory markers are also candidates as biomarkers to aid in the development of more effective and personalized treatment and prevention of psychiatric disorders [1]. Elevated biomarkers of inflammation, including cytokines and acute phase proteins, have been found in depressed patients.

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The administration of inflammatory substances like interferon in the treatment of hepatitis has been associated with development of depressive symptoms [2]. Leukocytes and other types of cells produce proteins or glycoproteins, termed cytokines, that serve as chemical communicators between cells and as autocrine signals on the cell producing the cytokine [3].

There is communication between nerves and immune cells, and this is known to play a role in cytokine production [3]. Evidence from other studies suggests a role of the immune system in a number of psychiatric disorders [4,5]. Cytokines are also known to produce symptoms of psychiatric sickness behaviour [6], causing reduced functional level. Another study show a reverse relationship where psychological stress can trigger cytokine release [7].

Different publications study and report on different cytokines in relation to psychiatric disorders. This is in line with our limited knowledge on the function and interplay of different cytokines in regulating activities in cells. Thus, the present state of art in this research field is to explore more cytokines at a time. This approach also opens for a bottom up chance to identify important subgroups of psychiatric patients where immune activity is relevant [8,9].

General psychiatric diagnoses have low reliability. The syndromal classification of the diagnostic systems International Statistical Classification of Diseases and Related Health Problems 10th revision (ICD-10), ICD-11 and the Diagnostic and Statistical Manual of Mental Disorders 5th edition (DSM-5) are descriptive, i.e., without emphasis to aetiology and pathogenesis. The diagnostic categories are wide and often non-specific, masking differences within the groups [10,11]. The heterogeneity of psychiatric disorders could in part be due to their multi-factorial nature [12]. There is a very high rate of co-occurrence of symptoms among some disorders [8]. In this context, inflammation does not seem to have diagnostic specificity. Addressing the above phenomena, some studies have examined relationships between immune function, brain functions, and associated neuropsychiatric symptoms, as opposed to categorical psychiatric diagnoses [1,13]. There are a few reports on altered levels of biomarkers in relation to specific symptoms rather than diagnostic groups, e.g., anhedonia and cytokines [13], C-reactive protein (CRP) as measured by high sensitive technology (hs-CRP) and monocyte chemoattractant protein-1 (MCP-1) in fatigue [14], brain derived neurotropic factor (BDNF) and general psychiatric symptoms [15], transforming growth factor (TGF) and aggression [16], C-C motif chemokine ligand 5 (CCL5) and in drug naïve children with attention deficit hyperactivity disorder (ADHD) [17] and atypical vs. typical symptom patterns in depression [18]. The complement system with activation of complement components is also suggested to play a role in immune-inflammation of major depressive disorder [19].

Therefore, the aim of this study was to explore if there are associations between cytokines, using multiplex analysis, and psychiatric symptom clusters, in terms of psychiatric symptoms across psychiatric diagnoses and boundaries.

METHODS

Participants

The population has been previously described [15]. In this cross-sectional study a total of 138 patients were recruited from an open in-patient general psychiatric ward, including patients mainly with affective and anxiety disorders, at the Department of Mental Health and Addiction, Nordland Hospital Trust, Bodoe, Norway. Six participants were excluded due to incomplete data sets. Patients aged 18 years and above were recruited consecutively in the period February 2014 to February 2018. Patients were referred from the hospital's outpatient services and from general practitioners. Patients not giving their consent and not understanding the Norwegian language or who were otherwise unable to give informed consent were excluded.

Ethics

A research nurse informed eligible patients about the study and written informed consent was obtained by a doctor administering the clinical assessments. The study was approved by the Regional Ethics Committee (notification 2015/1809/REK Nord).

Data Collection and Assessment of Psychiatric Symptoms

Weight, height and smoking data were obtained. Age and sex were derived from the hospital's personal identification data. All the patients were assessed by the main investigator (first author) upon consultation approximately one week after admission to the ward. At assessment the symptom check list 90 (SCL-90-R) was administered. This is a validated 90 item rating scale for monitoring

symptoms and symptom clusters experienced by the patient over the last week. SCL-90-R is psychometrically valid for measuring psychological status, measuring change in outcome studies, or screening for mental disorders. Each of the 90 items is rated on a five-point scale, ranging from, not at all (0) to extremely (4) [20]. The 90 single items are often grouped as primary dimensions or clusters: depression, somatization, obsessive-compulsive, interpersonal sensitivity, anxiety, anger-hostility, phobic-anxiety, paranoid ideation, and psychoticism. All symptom clusters are measured with raw scores in our study. The global severity index provides measures of overall psychological distress. We stratified the sample in two subgroups: those using psychotropic medication regularly and those not using psychotropic medication [15].

Biological Measures

Biological measures have been previously described [15]. Blood samples from the patients were obtained by trained technicians on the morning the day of assessment between 08:00 to 10:00 a.m., after approximately 12 hours of fasting and rest. Biochemical measures were performed at the Department of Laboratory Medicine, Nordland Hospital Trust. For measurement of serum cytokines, blood was withdrawn in Vacuette serum tubes, left for 30 minutes before centrifugation 10 minutes at 2,300 × *g* (3,500 rpm). Serum (2 × 1 ml) was stored in Matrix tubes on ice up to 2 hours before freezing at −80°C.

Cytokine analyses were performed by multiplex technology with a predefined kit Bio-Plex Human Cytokine 27-Plex Panel (Bio-Rad Laboratories Inc.) according to the instructions of the manufacturer. The assay detected the following interleukins, chemokines and growth factors: IL-1β, IL-1 receptor antagonist (IL-1ra), IL-2, IL-4, IL-5, IL-6, IL-7, IL-8 (C-X-C motif chemokine ligand 8; CXCL8), IL-9, IL-10, IL-12, IL-13, IL-15, IL-17, eotaxin-1 (C-C motif chemokine ligand 11; CCL11), basic fibroblast growth factor (bFGF), granulocyte-colony stimulating factor (G-CSF), granulocyte macrophage colony stimulating factor (GM-CSF), interferon (IFN)-gamma, interferon-inducible protein (IP-10) or (C-X-CL chemokine 10; CXCL10), MCP-1 or CCL2, macrophage inflammatory protein-1α (MIP-1α or CCL3), macrophage inflammatory protein-1-β (MIP-1β or CCL4), platelet derived growth factor-BB (PDGF-BB), regulated upon activation T cell expressed and secreted (RANTES), tumour necrosis factor (TNF), and vascular endothelial growth factor (VEGF). In addition, TGF-β1 was analysed with human Quantikine ELISA Kit (R&D Systems) according to the instructions from the manufacturer.

Some cytokines had high frequency of non-detectable levels and were therefore excluded in the statistical analyses. RANTES and PDGF results were affected by release from blood platelets *in vitro*, and were also excluded from further investigation. Therefore, the nine analysed cytokines were: TGF-β1, TNF, IL-1ra, IL-8, IL-9, MCP-1, IP-10, eotaxin and MIP-1β.

Statistical Analysis

Multiple linear regression analysis was performed using serum 27-multiplex cytokines and TGF-β1 as dependent variables and symptom clusters as well as confounding factors as body mass index (BMI), smoking, age and sex as independent variables. For all analyses the IBM-SPSS version 28.0 (IBM Co.) was used, and the statistical significance was set at $p < 0.01$ due to multiple comparisons.

RESULTS

Demographics

The characteristics of participants are presented in Table 1. Among the 132 patients there were 84 female and 48 male with a mean age of 37 years. A total of 102 patients of the 132 were using psychotropic medication, with antidepressants (n = 87) as the most commonly used. Patients were recruited over a 4-year period.

Biological Measures

The nine cytokines selected for further analyse (see Method) were: TGF-β1, TNF, IL-1ra, IL-8, IL-9, MCP-1, IP-10, eotaxin and MIP-1β. Cytokine levels are presented in Table 2.

Table 1. Characteristics of study participants

Variable	Value	Mean	Standard deviation
Sex (male)	47 (36)		
Smoking	60 (46)		
BMI	15, 55	28	7
Age (yr)	18, 78	37	14

Values are presented as number (%) or minimum, maximum.
BMI, body mass index.

Table 2. Descriptive statistics of the serum cytokines

Cytokine (pg/ml)	Mean serum level	Median serum level	Minimum	Maximum	Standard deviation
TGF-β1	25,107	23,438	6,995	60,137	9,288
TNF	27	22	13	164	15
IL-1ra	319	213	8	3,445	429
IL-8	13	12	5	42	7
IL-9	22	12	5	1,269	110
MCP-1	88	86	5	246	44
IP-10	4,622	3,908	1,574	18,573	2,570
Eotaxin	144	118	29	568	90
MIP-1β	133	129	90	328	29

TGF, transforming growth factor; TNF, tumour necrosis factor; IL, interleukin; MCP, monocyte chemoattractant protein; IP-10, interferon-gamma inducible protein 10; MIP, macrophage inflammatory protein.

Psychotropic Medication

Fourteen out of the 102 patients using regular psychotropic medication used a combination of either antidepressive medication and benzodiazepines/z-hypnotics, or antidepressive medication and antipsychotic medication. Eight patients used a combination of antidepressive medication and benzodiazepines/z-hypnotics, and six used the combination of antidepressive and antipsychotic medication.

Since this is an inpatient ward for patients with general psychiatric disorders and not for patients with psychotic disorders, we presume the use of antipsychotic medication to be off-label use, to improve sleep and reduce agitation [15].

Psychometrics

Our participants had highest scores on depression, obsessive- compulsive, somatization, and anxiety symptom clusters in SCL-90 (Table 3).

Table 3. Range of symptom clusters, raw-scores from SCL-90-R

Symptom clusters	Mean	Minimum	Maximum
Depression	27	0	46
Somatization	19	0	46
Anxiety	17	0	37
Phobic anxiety	10	0	25
Paranoid ideation	7	0	20
Anger hostility	4	0	21
Psychotisism	9	0	30
Obsessive compulsive	20	0	38
Interpersonal sensitivity	16	0	35
Global severity index	12	0	22

SCL-90-R, symptom check list 90-R.

Multiple Linear Regression Analysis

Cytokines were set as dependent variables and symptom clusters and confounding factors as predictors.

IL-1ra and IP-10 were positively associated with the anger hostility cluster (p = 0.007 and 0.001, respectively) (Table 4). Since cytokines are not expected to have a normal distribution, we $\log_{10}$-transformed IL-1ra and IP-10. The cytokine IL-1ra was no longer significant when log transformed ($\log_{10}$ IL-1ra: p = 0.787, 95% confidence interval [CI]: −0.02 to 0.26, β coefficient: 0.02). IP-10 was still significant after removal of one extreme outlier with the value 18,573 pg/ml, p = 0.001. After $\log_{10}$ transformation IP-10 remained significant ($\log_{10}$ IP-10: p = 0.009, 95% CI: 0.004 to 0.025, β coefficient: 0.24). Of note, none of the other cytokines had p values in this range; all were > 0.05 and only three observations were between 0.10 and 0.07 (Table 4).

These results remained significant when adjusting for age, sex, smoking and BMI.

Further we used split files for psychotropic medications and analysed $\log_{10}$ IP-10 and anger hostility symptom cluster in two subgroups; with or without psychotropic medication. Descriptive statistics are shown in Tables 5 and 6. Among patients using psychotropic medication we found a positive association between $\log_{10}$ transformed IP-10 and anger hostility (p = 0.002, 95% CI: 0.008 to 0.032, β coefficient: 0.32). We did not find any such association among patients not using psychotropic medication (p = 0.880, 95% CI: −0.024 to 0.021, β coefficient: −0.33).

Table 4. Multiple linear regression analysis of cytokines and symptom clusters, adjusted for age, sex, BMI and smoking

(A)

Cytokine	Somatization			Depression			Anxiety			Phobic anxiety			Paranoid		
	Coef.	95% CI	*p* value	Coef.	95% CI	*p* value	Coef.	95% CI	*p* value	Coef.	95% CI	*p* value	Coef.	95% CI	*p* value
TGF-β1	−0.91	−208 to 93	0.297	0.02	−124 to 182	0.837	−0.08	−264 to 123	0.410	−0.16	−392 to 47	0.094	−0.03	−356 to 340	0.786
TNF	−0.11	−0.3 to 0.2	0.288	0.03	−0.1 to 0.1	0.725	−0.13	−0.6 to 0.1	0.158	−0.09	−0.6 to 0.2	0.341	−0.10	−0.8 to 0.3	0.286
IL-1Ra	−0.01	−5.9 to 8.3	0.971	−0.14	−9.9 to 4.4	0.129	−0.10	−9.8 to 4.2	0.265	−0.08	−12 to 10	0.372	−0.09	−19 to 13	0.340
IL-8	0.01	−0.1 to 0.2	0.936	0.07	−0.4 to 0.2	0.456	−0.06	−0.2 to 0.2	0.488	−0.01	−0.1 to 0.2	0.954	−0.09	−0.3 to 0.2	0.039
IL-9	−0.20	−3.1 to 0.5	0.093	−0.03	−1.9 to 0.5	0.776	−0.05	−2.7 to 2.0	0.597	−0.10	−4.1 to 1.8	0.279	−0.04	4.5 to 3.9	0.660
MCP-1	−0.10	−1.1 to 0.3	0.226	−0.08	−0.9 to 0.3	0.397	0.06	−0.6 to 1.2	0.506	0.10	−0.4 to 1.8	0.292	−0.03	−1.6 to 1.6	0.800
IP-10	0.10	−16 to 55	0.338	0.09	−15 to 52	0.337	0.04	−36 to 61	0.641	0.04	−46 to 82	0.696	−0.04	−102 to 82	0.657
Eotaxin	0.01	−1.3 to 1.4	0.959	−0.03	−1.4 to 1.2	0.732	0.03	−1.3 to 2.1	0.789	−0.01	−2.0 to 2.3	0.981	0.02	−2.5 to 3.5	0.821
MIP-1β	−0.14	−0.8 to 0.1	0.144	0.07	−0.3 to 0.7	0.479	−0.03	−0.7 to 0.5	0.736	−0.10	−1.1 to 0.4	0.285	−0.04	−1.3 to 0.8	0.678

(B)

Cytokine	Anger hostility			Psychotisism			Obsessive comp			Interpersonal sensitivity			Global severity index		
	Coef.	95% CI	*p* value	Coef.	95% CI	*p* value	Coef.	95% CI	*p* value	Coef.	95% CI	*p* value	Coef.	95% CI	*p* value
TGF-β1	−0.09	−641 to 289	0.346	0.04	−191 to 343	0.649	0.01	−160 to 240	0.901	−0.03	−266 to 178	0.719	0.02	−386 to 293	0.816
TNF	−0.01	−0.8 to 0.3	0.901	−0.03	−0.6 to 0.3	0.776	−0.08	−0.4 to 0.2	0.380	−0.06	−0.5 to 0.2	0.502	0.05	−0.4 to 0.7	0.605
IL-1Ra	0.24	11 to 53	0.007	−0.15	−16.0 to 3.1	0.070	−0.09	−11.1 to 7.4	0.349	−0.13	−12.9 to 6.3	0.165	−0.11	−21 to 9	0.225
IL-8	−0.08	−0.4 to 0.3	0.398	−0.15	−0.4 to 0.3	0.098	0.02	−0.1 to 0.2	0.805	−0.03	−0.2 to 0.2	0.781	−0.07	−0.3 to 0.2	0.406
IL-9	−0.10	−8.0 to 3.2	0.285	−0.01	−3.1 to 3.3	0.958	−0.09	−3.2 to 1.6	0.349	−0.02	−2.5 to 2.4	0.808	0.07	−1.8 to 6.4	0.423
MCP-1	−0.10	−3.1 to 1.3	0.272	−0.05	−1.5 to 1.0	0.570	−0.02	−0.8 to 1.1	0.980	−0.76	−1.2 to 0.7	0.405	0.04	−2.3 to 2.0	0.660
IP-10	0.30	87 to 328	0.001	−0.02	−66 to 67	0.831	−0.01	−51 to 57	0.956	−0.03	−60 to 52	0.743	0.10	−37.9 to 127.8	0.278
Eotaxin	−0.14	−6.9 to 1.3	0.122	−0.09	−3.3 to 1.4	0.330	−0.54	−2.3 to 1.5	0.571	−0.08	−2.6 to 1.4	0.383	0.06	−1.7 to 5.0	0.514
MIP-1β	−0.11	−2.4 to 0.5	0.229	−0.02	−0.9 to 0.8	0.867	−0.04	−0.8 to 0.5	0.694	−0.00	−0.6 to 0.7	0.977	0.11	−0.5 to 1.7	0.227

BMI, body mass index; Coef., coefficient; CI, confidenceinterval; TGF, transforming growth factor; TNF, tumour necrosis factor; IL, interleukin; MCP, monocyte chemoattractant protein; IP-10, interferon-gamma inducible protein 10; MIP, macrophage inflammatory protein.

Table 5. Descriptive statistics on patients using psychotropic medication, with log_{10} IP-10 and anger hostility cluster

Variable	Mean	Standard deviation
BMI	27.8	5.8
Age	37.9	13.2
Sex	1.7	0.5
Smoking	1.5	0.5
Log_{10} IP-10	3.6	0.2
Anger hostility	3.6	3.5

IP-10, interferon-gamma inducible protein 10; BMI, body mass index.

Table 6. Descriptive statistics on patients not using psychotropic medication, with log_{10} IP-10 and anger hostility cluster

Variable	Mean	Standard deviation
BMI	29.2	9.5
Age	33.7	14.4
Sex	1.6	0.5
Smoking	1.7	0.5
Log_{10} IP-10	3.6	0.2
Anger hostility	4.1	3.6

IP-10, interferon-gamma inducible protein 10; BMI, body mass index.

DISCUSSION

In this study of patients with diverse general psychiatric diagnoses, serum IP-10 was positively associated (p = 0.009) with intensity of one symptom cluster in SCL-90; the anger hostility cluster. The finding was repeated in the subgroup of patients using psychotropic medication (p = 0.002) but not in the subgroup not using psychotropic medication (p = 0.880). The findings were consistent after correction for confounders and with a conservative level of significance accounting for multiple testing adjusting for multiple testing. None of the other analysed cytokines, chemokines or growth factors showed significant group differences.

IP-10 (interferon gamma induced protein 10) belongs to the CXC chemokine family. Chemokines are a group of immune mediators known to mediate cell migration. IP-10 binds to its CXCR3 receptor to induce chemotaxis as well as apoptosis, cell growth and angiostasis [21]. Alterations in IP-10 levels have been associated with inflammatory diseases including infectious diseases, immune dysfunction and tumour development. IP-10 is also suggested to play a role in heart failure and in mortality risk in general [21,22].

The role of IP-10 in migration and growth of cells also implies a potential role in neurogenesis in brain development, as well as recovery from disease of the brain [23]. IP-10 appears increased in patients with major depressive disorder and is reduced after treatment with antidepressants [24]. There also are reports on an association between IP-10 and depressive symptoms as well as sickness behaviour, cognitive impairment, fatigue and mood changes [25,26]. In a recent study on pregnant patients with high levels of anxiety and depressive symptoms, IP-10 was significantly increased [27]. In older patients with neuropsychiatric disorders, serum IP-10 was associated with sleep disturbances [28].

Several other studies that included IP-10 among analysed immune mediators however failed to find any association between IP-10 and diagnoses [29-32], or symptoms [16]. These and multiple others [13,26,33] reports associations with other cytokines for which we find no associations (e.g., IL-8, IL-6). This emphasises the need for further well powered studies before any conclusions can be drawn. There may, however be explanations for these variable findings. First, most studies explore distinct diagnoses with strict inclusion criteria in homogeneous samples [34]. We explored a diagnostically heterogenous population with few exclusion criteria. Our previous report on increased BDNF in a non-medicated subgroup indicates effects of severity of general psychiatric disorders as well as potentially medications, known to affect immune status and cytokine levels. In addition to differences in patient populations, there may be methodological factors contributing to bias and inconsistency in the field [35]. A lack of standardization for biological, blood collecting and methodological variables across different laboratories as well as studies, are likely influences driving inconsistent findings in the field [36,37].

Apart from the above-mentioned studies, there are few reports on the association between IP-10 and symptoms and psychiatric diagnoses. Given the role of chemokines like IP-10 in cell growth and migration this chemokine merits further study.

Antidepressants are supposed to exert their effect on depression by regulating neurotransmitters. They do however also have immune regulatory properties, being both pro-and anti-inflammatory [38,39]. A meta-analysis revealed that persistent elevation of TNF was associated with poorer clinical outcome of antidepressant treatment

in depressed patients, and a decrease of IL-6 independent of clinical outcome [40]. Some studies show that antidepressant therapies significantly decrease IP-10 production after 8 weeks of treatment, but the symptoms of anger hostility were not investigated [41,42]. In non-responders to antidepressant treatment immune activity may play a role. Better mood outcomes were associated with a healthier immune-response after treatment [43].

This and our previous study [15], suggest that patients receiving psychotropic medication differ from those not receiving psychotropic medication regarding cytokines and growth factors. The effect of psychotropic medication as well as severity of symptoms on cytokines and growth factors do however need further exploration.

We did not study a distinct diagnostic group, but the defined symptom clusters in SCL-90 across diagnostic groups. In general, the cluster anger hostility in SCL-90 provide evidence of satisfactory validity and reliability [44,45]. Anger refers to emotional state encompassing feelings ranging from mild annoyance to intense fury and anger, accompanied by autonomic nervous system stimulation. Hostility is constituted as a belief, expectation and negative attitudes toward persons and things. Anger hostility appears to be a risk factor for health and psychological wellbeing [44].

Anger and hostility are symptoms seen in several psychiatric diagnostic groups including depression, anxiety, psychoses, mania. They also are common phenomena seen in people who are tired, under stress etc. Animal experiments have revealed a direct effect of cytokines in certain areas of the brain on aggression [46]. In support of this several studies have shown that anger and hostility are increased in patients receiving repeated cytokine immunotherapy, supporting the view that cytokines may facilitate the expression of aggressive behaviour in humans [47,48].

Hostility may be a phenotypic risk factor linked to adverse health outcome and cytokines have been suggested to mediate this relationship. There is some evidence that hostility is related to a pro-inflammatory cytokine profile and adverse health outcomes, and may thus serve as a mediating factor [49].

Depression and cardiovascular disease and diabetes type 2 – all associated to inflammation – as well as hypertension show increased expression of anger and hostility [49-51]. Larsen *et al.* [52] found other cytokines associated to aggression and activation, respectively, in an acute psychiatric population indicating some immune activation that may also be causal, though so far with non-conclusive findings.

There are several limitations to this study. We do not have any information on the length of psychotropic medication, nor the individual patient's response to psychotropic therapy. Further, we did not study cytokines in relation to diagnoses and compared to a healthy control group. However, we are still able to compare psychiatric symptoms with a panel of cytokines, adjusting for confounding factors. The cross-sectional design is another limitation, making it impossible to draw any conclusion and causal connection between cytokines and symptom clusters. A further limitation might be that the presence of other physical illnesses and medication was not considered in this study. Also, blood pressure and other clinical assessments for cardiovascular disease were not conducted. However, these patients were not acutely ill somatically and their main complaint for admission were general psychiatric disorders like affective and anxiety disorders. There was no reported evidence of fever or acute somatic illness when blood samples were drawn upon clinical examination by a medically doctor. We did not consider substance abuse, but severe substance abuse would not fit with referral to this ward.

The main originality of the study is the focus on symptoms and symptom clusters across diagnostic boundaries. We adjusted for smoking, age, sex and BMI. The sample size appears adequate (n = 132), based on Tabachnick and Fidell's sample size requirements for multiple regression [53]. Regarding the biological measures, serum was sampled after rest and fasting in the morning to control for effects of diurnal variation [54]. Another strength of the study is that data were sampled roughly one week after admission to reduce potential stress achieved by the admission itself and to reduce any possible stress-induced alterations in the biomarkers. During these first days, patients will also have been exposed to care, safety, professional milieu therapy, psychotherapy, and often improved sleep and nutrition, all of which may reduce the possible stress of admission to the inpatient setting. The laboratory used a standardized protocol for analysis and with one experienced technician performing the laboratory analysis.

The significant positive association between the symp-

tom cluster anger hostility and IP-10 suggests that this symptom cluster might be an independent transdiagnostic entity associated with this cytokine.

Our findings suggest that there is a selective positive association between IP-10 and anger hostility symptom cluster, independent of diagnostic groups in an inpatient population with general psychiatric disorders. The IP-10 association with intensity of anger hostility was further restricted to the patients using psychotropic medication. Anger hostility can be a risk factor for adverse health outcome, and cytokines has been suggested to mediate this relationship. This novel finding may indicate a biological relation between increase serum IP-10 and anger hostility.

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■ Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

■ Author Contributions

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REFERENCES

1. Miller AH, Haroon E, Raison CL, Felger JC. *Cytokine targets in the brain: impact on neurotransmitters and neurocircuits. Depress Anxiety 2013;30:297-306.*
2. Haroon E, Raison CL, Miller AH. *Psychoneuroimmunology meets neuropsychopharmacology: translational implications of the impact of inflammation on behavior. Neuropsychopharmacology 2012;37:137-162.*
3. Salvador AF, de Lima KA, Kipnis J. *Neuromodulation by the immune system: a focus on cytokines. Nat Rev Immunol 2021;21:526-541.*
4. Conti CM, Fulcheri M. *Interlationship between psychology and cytokines. J Biol Regul Homeost Agents 2010;24:485-490.*
5. Yuan N, Chen Y, Xia Y, Dai J, Liu C. *Inflammation-related biomarkers in major psychiatric disorders: a cross-disorder assessment of reproducibility and specificity in 43 meta-analyses. Transl Psychiatry 2019;9:233.*
6. Dantzer R, O'Connor JC, Freund GG, Johnson RW, Kelley KW. *From inflammation to sickness and depression: when the immune system subjugates the brain. Nat Rev Neurosci 2008;9:46-56.*
7. Takahashi A, Flanigan ME, McEwen BS, Russo SJ. *Aggression, social stress, and the immune system in humans and animal models. Front Behav Neurosci 2018;12:56.*
8. Hyman SE. *Grouping diagnoses of mental disorders by their common risk factors. Am J Psychiatry 2011;168:1-3.*
9. van Beveren NJ, Hoogendijk WJ. *Clinical utility of serum biomarkers for major psychiatric disorders. Int Rev Neurobiol 2011;101:351-374.*
10. Bebbington P. *Categories, continua and the growth of psychi-*

atric knowledge. Soc Psychiatry Psychiatr Epidemiol 2015; 50:507-510.

11. Anderson G, Berk M, Maes M. *Biological phenotypes underpin the physio-somatic symptoms of somatization, depression, and chronic fatigue syndrome. Acta Psychiatr Scand 2014;129:83-97.*
12. Lakhan SE, Vieira K, Hamlat E. *Biomarkers in psychiatry: drawbacks and potential for misuse. Int Arch Med 2010;3:1.*
13. Freed RD, Mehra LM, Laor D, Patel M, Alonso CM, Kim-Schulze S, *et al. Anhedonia as a clinical correlate of inflammation in adolescents across psychiatric conditions. World J Biol Psychiatry 2019;20:712-722.*
14. Groven N, Fors EA, Reitan SK. *Patients with Fibromyalgia and Chronic Fatigue Syndrome show increased hsCRP compared to healthy controls. Brain Behav Immun 2019;81:172-177.*
15. Soloey-Nilsen H, Nygaard-Odeh K, Kristiansen MG, Brekke OL, Mollnes TE, Reitan SK, *et al. Association between brain-derived neurotropic factor (BDNF), high-sensitivity C-reactive protein (hs-CRP) and psychiatric symptoms in medicated and unmedicated patients. BMC Psychiatry 2022;22:84.*
16. Larsen JB, Stunes AK, Vaaler A, Reitan SK. *Cytokines in agitated and non-agitated patients admitted to an acute psychiatric department: a cross-sectional study. PLoS One 2019;14: e0222242.*
17. Özaslan A, Güney E, Gülbahar Ö, Büyüktaskin D, Arslan B. *Increased serum level of CCL5 in children with attention-deficit/hyperactivity disorder: first results about serum chemokines. Clin Psychopharmacol Neurosci 2022;20:109-117.*
18. Milaneschi Y, Lamers F, Berk M, Penninx B. *Depression heterogeneity and its biological underpinnings: toward immunometabolic depression. Biol Psychiatry 2020;88:369-380.*
19. Reddy PV, Talukdar PM, Subbanna M, Bhargav PH, Arasappa R, Venkatasubramanian G, *et al. Multiple complement pathway-related proteins might regulate immunopathogenesis of major depressive disorder. Clin Psychopharmacol Neurosci 2023;21:313-319.*
20. Schmitz N, Hartkamp N, Kiuse J, Franke GH, Reister G, Tress W. *The Symptom Check-List-90-R (SCL-90-R): a German validation study. Qual Life Res 2000;9:185-193.*
21. Leavitt C, Zakai NA, Auer P, Cushman M, Lange EM, Levitan EB, *et al. Interferon gamma-induced protein 10 (IP-10) and cardiovascular disease in African Americans. PLoS One 2020; 15:e0231013.*
22. Liu M, Guo S, Hibbert JM, Jain V, Singh N, Wilson NO, *et al. CXCL10/IP-10 in infectious diseases pathogenesis and potential therapeutic implications. Cytokine Growth Factor Rev 2011;22:121-130.*
23. Stuart MJ, Baune BT. *Chemokines and chemokine receptors in mood disorders, schizophrenia, and cognitive impairment: a systematic review of biomarker studies. Neurosci Biobehav Rev 2014;42:93-115.*
24. Wong ML, Dong C, Maestre-Mesa J, Licinio J. *Polymorphisms in inflammation-related genes are associated with susceptibility to major depression and antidepressant response. Mol Psychiatry 2008;13:800-812.*
25. Blank T, Detje Claudia N, Spieß A, Hagemeyer N, Brendecke Stefanie M, Wolfart J, *et al. Brain endothelial- and epithelial-specific interferon receptor chain 1 drives virus-induced sickness behavior and cognitive impairment. Immunity 2016;44: 901-912.*
26. Kiecolt-Glaser JK, Derry HM, Fagundes CP. *Inflammation: depression fans the flames and feasts on the heat. Am J Psychiatry 2015;172:1075-1091.*
27. Camacho-Arroyo I, Flores-Ramos M, Mancilla-Herrera I, Cruz FMC, Hernández-Ruiz J, Diaz GP, *et al. Chemokine profile in women with moderate to severe anxiety and depression during pregnancy. BMC Pregnancy Childbirth 2021;21:807.*
28. Clark C, Richiardi J, Maréchal B, Bowman GL, Dayon L, Popp J. *Systemic and central nervous system neuroinflammatory signatures of neuropsychiatric symptoms and related cognitive decline in older people. J Neuroinflammation 2022;19: 127.*
29. Gaarden TL, Engedal K, Benth J, Larsen M, Lorentzen B, Mollnes TE, *et al. Exploration of 27 plasma immune markers: a cross-sectional comparison of 64 old psychiatric inpatients having unipolar major depression and 18 non-depressed old persons. BMC Geriatr 2018;18:149.*
30. Benedetti F, Poletti S, Hoogenboezem TA, Locatelli C, de Wit H, Wijkhuijs AJM, *et al. Higher baseline proinflammatory cytokines mark poor antidepressant response in bipolar disorder. J Clin Psychiatry 2017;78:e986-e993.*
31. Poletti S, Leone G, Hoogenboezem TA, Ghiglino D, Vai B, de Wit H, *et al. Markers of neuroinflammation influence measures of cortical thickness in bipolar depression. Psychiatry Res Neuroimaging 2019;285:64-66.*
32. Simon NM, McNamara K, Chow CW, Maser RS, Papakostas GI, Pollack MH, *et al. A detailed examination of cytokine abnormalities in Major Depressive Disorder. Eur Neuropsychopharmacol 2008;18:230-233.*
33. Hoge EA, Brandstetter K, Moshier S, Pollack MH, Wong KK, Simon NM. *Broad spectrum of cytokine abnormalities in panic disorder and posttraumatic stress disorder. Depress Anxiety 2009;26:447-455.*
34. Goldsmith DR, Rapaport MH, Miller BJ. *A meta-analysis of blood cytokine network alterations in psychiatric patients: comparisons between schizophrenia, bipolar disorder and depression. Mol Psychiatry 2016;21:1696-1709.*
35. Carvalho AF, Köhler CA, Fernandes BS, Quevedo J, Miskowiak KW, Brunoni AR, *et al. Bias in emerging biomarkers for bipolar disorder. Psychol Med 2016;46:2287-2297.*
36. Skibinska M, Kapelski P, Rajewska-Rager A, Pawlak J, Szczepankiewicz A, Narozna B, *et al. Brain-derived neurotrophic factor (BDNF) serum level in women with first-episode depression, correlation with clinical and metabolic parameters. Nord J Psychiatry 2018;72:191-196.*
37. Hennø LT, Storjord E, Christiansen D, Bergseth G, Ludviksen

JK, Fure H, *et al. Effect of the anticoagulant, storage time and temperature of blood samples on the concentrations of 27 multiplex assayed cytokines - consequences for defining reference values in healthy humans. Cytokine 2017;97:86-95.*

38. Schmidt FM, Kirkby KC, Lichtblau N. *Inflammation and immune regulation as potential drug targets in antidepressant treatment. Curr Neuropharmacol 2016;14:674-687.*
39. Munzer A, Sack U, Mergl R, Schönherr J, Petersein C, Bartsch S, *et al. Impact of antidepressants on cytokine production of depressed patients in vitro. Toxins (Basel) 2013;5:2227-2240.*
40. Strawbridge R, Arnone D, Danese A, Papadopoulos A, Herane Vives A, Cleare AJ. *Inflammation and clinical response to treatment in depression: a meta-analysis. Eur Neuropsychopharmacol 2015;25:1532-1543.*
41. Tsai JH, Kuo CH, Yang P, Cheng KH, Wang PW, Chen CC, *et al. Effects of antidepressants on IP-10 production in LPS-activated THP-1 human monocytes. Int J Mol Sci 2014;15:13223-13235.*
42. de la Peña FR, Cruz-Fuentes C, Palacios L, Girón-Pérez MI, Medina-Rivero E, Ponce-Regalado MD, *et al. Serum levels of chemokines in adolescents with major depression treated with fluoxetine. World J Psychiatry 2020;10:175-186.*
43. Syed SA, Beurel E, Loewenstein DA, Lowell JA, Craighead WE, Dunlop BW, Mayberg HS, *et al. Defective inflammatory pathways in never-treated depressed patients are associated with poor treatment response. Neuron 2018;99:914-924.e3.*
44. Cavalcanti J, Moura G, Pimentel C. *Psychometric parameters of the subscale of hostility from the Symptom Checklist 90 (SCL-90). Psico-USF 2019;24:373-381.*
45. Smits IAM, Timmerman ME, Barelds DPH, Meijer RR. *The Dutch Symptom Checklist-90-Revised: is the use of the subscales justified? Eur J Psychol Assess 2015;31:263-271.*
46. Siegel A, Bhatt S, Bhatt R, Zalcman SS. *The neurobiological bases for development of pharmacological treatments of aggressive disorders. Curr Neuropharmacol 2007;5:135-147.*
47. Kraus MR, Schäfer A, Faller H, Csef H, Scheurlen M. *Psychiatric symptoms in patients with chronic hepatitis C receiving interferon alfa-2b therapy. J Clin Psychiatry 2003;64:708-714.*
48. Pesce M, Speranza L, Franceschelli S, Ialenti V, Patruno A, Febo MA, *et al. Biological role of interleukin-1beta in defensive-aggressive behaviour. J Biol Regul Homeost Agents 2011;25:323-329.*
49. Pesce M, Speranza L, Franceschelli S, Ialenti V, Patruno A, Febo MA, *et al. Biological role of interleukin-1beta in defensive-aggressive behaviour. J Biol Regul Homeost Agents 2011;25:323-329.*
50. Koh KB, Kim CH, Park JK. *Predominance of anger in depressive disorders compared with anxiety disorders and somatoform disorders. J Clin Psychiatry 2002;63:486-492.*
51. Boyle SH, Jackson WG, Suarez EC. *Hostility, anger, and depression predict increases in C3 over a 10-year period. Brain Behav Immun 2007;21:816-823.*
52. Larsen JB, Stunes AK, Iversen VC, Vaaler AE, Reitan SK. *Cytokines in relation to motor activity in an acute psychiatric population. Front Psychiatry 2019;10:920.*
53. Harlow LL. *Book review of using multivariate statistics by Barbara G. Tabachnick and Linda S. Fidell. Struct Equ Modeling 2002;9:621-636.*
54. Haack M, Kraus T, Schuld A, Dalal M, Koethe D, Pollmächer T. *Diurnal variations of interleukin-6 plasma levels are confounded by blood drawing procedures. Psychoneuroendocrinology 2002;27:921-931.*