Transdiagnostic associations between anger hostility and chemokine interferon-gamma inducible protein 10 (CXCL 10)

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Research Article

Keywords: Immune system, cytokines, psychiatry, mental disorders, neuroscience, IP-10; interferon-gamma inducible protein, anger hostility

Posted Date: January 11th, 2023

DOI: https://doi.org/10.21203/rs.3.rs-2422199/v1

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Abstract

Background

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.

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.

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. 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 ICD – 10, ICD – 11 and 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], 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], and atypical vs typical symptom patterns in depression [17].

Therefore, the aim of this study was to explore if there are associations between cytokines, using multiplex analysis, and general psychiatric disorders, 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 gender 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. SCL90-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) [18]. 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 (GSI) provides measures of overall psychological distress.

Biological Measures (Dup: Abstract ?)

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 08:00–10:00 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 2300x g (3500 rpm). Serum (2x 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., Hercules, CA, USA) according to the instructions of the manufacturer. The assay detected the following interleukins, chemokines and growth factors: IL1β, IL1 receptor antagonist (IL1ra), IL2, IL4, IL5, IL6, IL7, IL8 (C-X-C motif chemokine ligand 8; CXCL8), IL9, IL10, IL12, IL13, 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-C chemokine 10; CXCL10), monocyte chemotactic protein (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, tumor growth factor (TGF-β1) was analysed with human Quantikine ELISA Kit (R&D Systems, Minneapolis, MN) 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-b1, 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 BMI, smoking, age and sex as independent variables. For all analyses the IBM-SPSS version 28.0 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 women and 48 men with a mean age of 37 years. A total of 102 patients were using psychotropic medication, with antidepressants (n = 87) as the most commonly used. Patients were recruited over a 4-year period.

<table>
<thead>
<tr>
<th>Gender (male)</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smoking</td>
<td>60</td>
<td>46</td>
</tr>
<tr>
<td>BMI</td>
<td>15</td>
<td>55</td>
</tr>
<tr>
<td>Age (years)</td>
<td>18</td>
<td>78</td>
</tr>
</tbody>
</table>

### 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>
<thead>
<tr>
<th>Cytokine</th>
<th>Mean serum level</th>
<th>Median serum level</th>
<th>Min</th>
<th>Max</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>TGF-b1</td>
<td>25107</td>
<td>23438</td>
<td>6995</td>
<td>60137</td>
<td>9288</td>
</tr>
<tr>
<td>TNF</td>
<td>27</td>
<td>22</td>
<td>13</td>
<td>164</td>
<td>15</td>
</tr>
<tr>
<td>IL-1ra</td>
<td>319</td>
<td>213</td>
<td>8</td>
<td>3445</td>
<td>429</td>
</tr>
<tr>
<td>IL-8</td>
<td>13</td>
<td>12</td>
<td>5</td>
<td>42</td>
<td>7</td>
</tr>
<tr>
<td>IL-9</td>
<td>22</td>
<td>12</td>
<td>5</td>
<td>1269</td>
<td>110</td>
</tr>
<tr>
<td>MCP-1</td>
<td>88</td>
<td>86</td>
<td>5</td>
<td>246</td>
<td>44</td>
</tr>
<tr>
<td>IP-10</td>
<td>4622</td>
<td>3908</td>
<td>1574</td>
<td>18573</td>
<td>2570</td>
</tr>
<tr>
<td>Eotaxin</td>
<td>144</td>
<td>118</td>
<td>29</td>
<td>568</td>
<td>90</td>
</tr>
<tr>
<td>MIP-1β</td>
<td>133</td>
<td>129</td>
<td>90</td>
<td>328</td>
<td>29</td>
</tr>
</tbody>
</table>

### Table 3

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

<table>
<thead>
<tr>
<th>Symptom Cluster</th>
<th>Mean</th>
<th>Minimum</th>
<th>Maximum</th>
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</thead>
<tbody>
<tr>
<td>Depression</td>
<td>27</td>
<td>0</td>
<td>46</td>
</tr>
<tr>
<td>Somatization</td>
<td>19</td>
<td>0</td>
<td>46</td>
</tr>
<tr>
<td>Anxiety</td>
<td>17</td>
<td>0</td>
<td>37</td>
</tr>
<tr>
<td>Phobic anxiety</td>
<td>10</td>
<td>0</td>
<td>25</td>
</tr>
<tr>
<td>Paranoid ideation</td>
<td>7</td>
<td>0</td>
<td>20</td>
</tr>
<tr>
<td>Anger hostility</td>
<td>4</td>
<td>0</td>
<td>21</td>
</tr>
<tr>
<td>Psychotisism</td>
<td>9</td>
<td>0</td>
<td>30</td>
</tr>
<tr>
<td>Obsessive compulsive</td>
<td>20</td>
<td>0</td>
<td>38</td>
</tr>
<tr>
<td>Interpersonal sensitivity</td>
<td>16</td>
<td>0</td>
<td>35</td>
</tr>
<tr>
<td>Global severity index</td>
<td>12</td>
<td>0</td>
<td>22</td>
</tr>
</tbody>
</table>
Psychometrics

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

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<sub>10</sub>-transformed IL-1ra and IP-10. The cytokine IL-1ra was no longer significant when log transformed (Lg10 IL-1ra; p = 0.787, 95% CI; -0.02-0.26, β coefficient; 0.02). IP-10 was still significant after removal of one extreme outlier with the value 18573 pg/ml, p = 0.001. After log<sub>10</sub> transformation IP-10 remained significant (Lg10 IP-10; p = 0.009, 95% CI; 0.004–0.025, 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.

<table>
<thead>
<tr>
<th>Cytokine</th>
<th>95% CI &gt; 0.05</th>
<th>Coef.</th>
<th>95% CI</th>
<th>p-val.</th>
<th>Coef.</th>
<th>95% CI</th>
<th>p-val.</th>
<th>Coef.</th>
<th>95% CI</th>
<th>p-val.</th>
<th>Coef.</th>
<th>95% CI</th>
<th>p-val.</th>
<th>Coef.</th>
<th>95% CI</th>
<th>p-val.</th>
</tr>
</thead>
<tbody>
<tr>
<td>TGF-b1</td>
<td>-0.91</td>
<td>-208-93</td>
<td>0.297</td>
<td>0.02</td>
<td>-124-182</td>
<td>0.837</td>
<td>-0.08</td>
<td>-264-123</td>
<td>0.410</td>
<td>-0.16</td>
<td>-392-47</td>
<td>0.094</td>
<td>-0.03</td>
<td>-356-340</td>
<td>0.786</td>
<td></td>
</tr>
<tr>
<td>TNF</td>
<td>-0.11</td>
<td>-0.3-0.2</td>
<td>0.288</td>
<td>0.03</td>
<td>-0.1-0.1</td>
<td>0.725</td>
<td>-0.13</td>
<td>-0.6-0.1</td>
<td>0.158</td>
<td>-0.09</td>
<td>-0.6-0.2</td>
<td>0.341</td>
<td>-0.10</td>
<td>-0.8-0.3</td>
<td>0.286</td>
<td></td>
</tr>
<tr>
<td>IL-1Ra</td>
<td>-0.91</td>
<td>-5.9-8.3</td>
<td>0.971</td>
<td>-0.14</td>
<td>-9.9-4.4</td>
<td>0.129</td>
<td>-0.10</td>
<td>-9.8-4.2</td>
<td>0.265</td>
<td>-0.08</td>
<td>-12-10</td>
<td>0.372</td>
<td>-0.09</td>
<td>-19-13</td>
<td>0.340</td>
<td></td>
</tr>
<tr>
<td>IL-8</td>
<td>0.01</td>
<td>-0.1-0.2</td>
<td>0.936</td>
<td>0.07</td>
<td>-0.4-0.2</td>
<td>0.456</td>
<td>-0.064</td>
<td>-0.2-0.2</td>
<td>0.488</td>
<td>-0.01</td>
<td>-0.1-0.2</td>
<td>0.954</td>
<td>-0.09</td>
<td>-0.3-0.2</td>
<td>0.039</td>
<td></td>
</tr>
<tr>
<td>IL-9</td>
<td>-0.20</td>
<td>-3.1-0.5</td>
<td>0.093</td>
<td>-0.03</td>
<td>-1.9-0.5</td>
<td>0.776</td>
<td>-0.05</td>
<td>-2.7-2.0</td>
<td>0.597</td>
<td>-0.10</td>
<td>-4.1-1.8</td>
<td>0.279</td>
<td>-0.04</td>
<td>4.5-3.9</td>
<td>0.660</td>
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<tr>
<td>MCP-1</td>
<td>-0.10</td>
<td>-1.1-0.3</td>
<td>0.226</td>
<td>-0.08</td>
<td>-0.9-0.3</td>
<td>0.397</td>
<td>0.06</td>
<td>-0.6-1.2</td>
<td>0.506</td>
<td>0.101</td>
<td>-0.4-1.8</td>
<td>0.292</td>
<td>-0.03</td>
<td>-1.6-1.6</td>
<td>0.800</td>
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<tr>
<td>IP-10</td>
<td>0.10</td>
<td>-16-55</td>
<td>0.338</td>
<td>0.09</td>
<td>-15-52</td>
<td>0.337</td>
<td>0.04</td>
<td>-36-61</td>
<td>0.641</td>
<td>0.04</td>
<td>-46-82</td>
<td>0.696</td>
<td>-0.04</td>
<td>-102-82</td>
<td>0.657</td>
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<tr>
<td>Eotaxin</td>
<td>0.01</td>
<td>-1.3-1.4</td>
<td>0.959</td>
<td>-0.03</td>
<td>-1.4-1.2</td>
<td>0.732</td>
<td>0.03</td>
<td>-1.3-2.1</td>
<td>0.789</td>
<td>-0.01</td>
<td>-2.0-2.3</td>
<td>0.981</td>
<td>0.02</td>
<td>-2.5-3.5</td>
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<tr>
<td>MIP-1β</td>
<td>-0.14</td>
<td>-0.8-0.1</td>
<td>0.144</td>
<td>0.07</td>
<td>-0.3-0.7</td>
<td>0.479</td>
<td>-0.03</td>
<td>-0.7-0.5</td>
<td>0.736</td>
<td>-0.10</td>
<td>-1.1-0.4</td>
<td>0.285</td>
<td>-0.04</td>
<td>-1.3-0.8</td>
<td>0.678</td>
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<tr>
<td>Anger hostility</td>
<td>Psychotisism</td>
<td>Obsessive comp</td>
<td>Interpersonal sensitivity</td>
<td>Global severity index</td>
<td></td>
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<tr>
<td>Coef.</td>
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<td>p-val</td>
<td>Coef.</td>
<td>95% CI</td>
<td>p-val</td>
<td>Coef.</td>
<td>95% CI</td>
<td>p-val</td>
<td>Coef.</td>
<td>95% CI</td>
<td>p-val</td>
<td></td>
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<td>TGF-b1</td>
<td>-0.09</td>
<td>-641-289</td>
<td>0.346</td>
<td>-0.191-343</td>
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<td>-160-240</td>
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<td>-266-178</td>
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<td>0.901</td>
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<td>-0.5-0.2</td>
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<td>-0.4-0.7</td>
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<tr>
<td>IL-1Ra</td>
<td>0.24</td>
<td>11-53</td>
<td>0.007</td>
<td>-16.0-3.1</td>
<td>0.070</td>
<td>-11.1-7.4</td>
<td>0.349</td>
<td>-12.9-6.3</td>
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<tr>
<td>IL-8</td>
<td>-0.08</td>
<td>-0.4-0.3</td>
<td>0.398</td>
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<td>IL-9</td>
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<td>0.285</td>
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<td>0.958</td>
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<tr>
<td>MCP-1</td>
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<td>-3.1-1.3</td>
<td>0.272</td>
<td>-1.5-1.0</td>
<td>0.570</td>
<td>-0.8-1.1</td>
<td>0.980</td>
<td>-1.2-0.7</td>
<td>0.405</td>
<td>0.04</td>
<td>-2.3-6.4</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IP-10</td>
<td>0.30</td>
<td>87-328</td>
<td>0.001</td>
<td>-66-67</td>
<td>0.831</td>
<td>-51-57</td>
<td>0.956</td>
<td>-60-52</td>
<td>0.743</td>
<td>0.10</td>
<td>-37.9-127.8</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Eotaxin</td>
<td>-0.14</td>
<td>-6.9-1.3</td>
<td>0.122</td>
<td>-3.3-1.4</td>
<td>0.330</td>
<td>-2.3-1.5</td>
<td>0.571</td>
<td>-2.6-1.4</td>
<td>0.383</td>
<td>0.06</td>
<td>-1.7-5.0</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MIP-1β</td>
<td>-0.11</td>
<td>-2.4-0.5</td>
<td>0.229</td>
<td>-0.9-0.8</td>
<td>0.867</td>
<td>-0.8-0.5</td>
<td>0.694</td>
<td>-0.6-0.7</td>
<td>0.977</td>
<td>0.11</td>
<td>-0.5-1.7</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 4

These results remained significant when adjusting for age, gender, 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; 0.008–0.032, β coefficient; 0.32). We did not find any such association among patients not using psychotropic medication ($p = 0.880$, 95% CI; -0.024–0.021, β coefficient; -0.33).

Table 5

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

<table>
<thead>
<tr>
<th>Mean</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI</td>
<td>27.8</td>
</tr>
<tr>
<td>Age</td>
<td>37.9</td>
</tr>
<tr>
<td>Gender</td>
<td>1.7</td>
</tr>
<tr>
<td>Smoking</td>
<td>1.5</td>
</tr>
<tr>
<td>Log_{10} IP-10</td>
<td>3.6</td>
</tr>
<tr>
<td>Anger hostility</td>
<td>3.6</td>
</tr>
</tbody>
</table>
Table 6
Descriptive statistics on patients not using psychotropic medication, with $\log_{10}$ IP-10 and anger hostility cluster.

<table>
<thead>
<tr>
<th></th>
<th>Mean</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI</td>
<td>29.2</td>
<td>9.5</td>
</tr>
<tr>
<td>Age</td>
<td>33.7</td>
<td>14.4</td>
</tr>
<tr>
<td>Gender</td>
<td>1.6</td>
<td>0.5</td>
</tr>
<tr>
<td>Smoking</td>
<td>1.7</td>
<td>0.5</td>
</tr>
<tr>
<td>$\log_{10}$ IP-10</td>
<td>3.6</td>
<td>0.2</td>
</tr>
<tr>
<td>Anger hostility</td>
<td>4.1</td>
<td>3.6</td>
</tr>
</tbody>
</table>

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 [19]. 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 [19, 20].

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 [21]. IP-10 appears increased in patients with major depressive disorder (MDD), and is reduced after treatment with antidepressants [22]. There also are reports on an association between IP-10 and depressive symptoms as well as sickness behaviour, cognitive impairment, fatigue and mood changes [23, 24]. In a recent study on pregnant patients with high levels of anxiety and depressive symptoms, IP-10 was significantly increased [25]. In older patients with neuropsychiatric disorders, serum IP-10 was associated with sleep disturbances [26].

Several other studies that included IP-10 among analysed immune mediators however failed to find any association between IP-10 and diagnoses [27–30], or symptoms [16]. These and multiple others [13, 24, 31] 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 [32]. 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 [33]. 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 [34, 35].

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 [36, 37]. 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 [38]. 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 [39, 40]. In non-responders to antidepressant treatment immune activity may play a role. Better mood outcomes were associated with a healthier immune-response after treatment [41].

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 [42, 43]. 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 [42].

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 [44]. 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 [45, 46].

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 [47].

Depression and cardiovascular disease and diabetes type 2 - all associated to inflammation – as well as hypertension show increased expression of anger and hostility [47–49]. Brun Larsen et al 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 [50].

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, gender and BMI. The sample size appears adequate (n = 132), based on Tabachnick and Fidell’s sample size requirements for multiple regression [51]. Regarding the biological measures, serum was sampled after rest and fasting in the morning to control for effects of diurnal variation [52]. 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 symptom cluster anger hostility and IP-10 suggests that this symptom cluster might be an independent transdiagnostic entity associated with this cytokine.

**Conclusion**

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.

**Abbreviations**

BMI, Body Mass Index; CI, confidence interval; SCL-90-R, Symptom Check List Revised; SPSS, Statistical Package for the Social Sciences, SD; Standard deviation, coefficient; standardized β coefficient, MDD; Major depressive disorder, IP-10; interferon-gamma inducible protein 10.

**Declarations**

**Funding**

This study was funded in part by a grant from Northern Norway Regional Health Authority.

**Availability of data/materials**
Our data contain individual personalized information such as personal numbers and name initials, it thus cannot be shared, but it can be available from the corresponding author on reasonable request.

**Author contributions**

HSN wrote the outline and the first draft of the article. All authors contributed to, and have approved the final manuscript.

**Competing interests**

The authors declared no conflicts of interests with respect to their authorship or publication of this article.

**Ethical approval and consent to participate**

The study was approved by the Regional Ethics Committee, notification 2015/1809/REK Nord.

All methods were carried out in accordance with relevant guidelines and regulations, and with written informed consent from all the patients included in the study. A research nurse informed eligible patients about the study and written informed consent was obtained by a doctor administering the clinical assessments [15].

**Acknowledgments**

We would like to thank Lill Magna Lekanger for preparing the data files as well as Hilde Myrvold and Ann-Torill Kokaas for patient coordination upon admittance. Judith Krey Ludvigsen and Evy Eide is also greatly acknowledged for analyzing biomarkers. We also thank Nina Groven for the advice and counselling with SPSS and data files as well as Tom Wilsgaard for statistical contribution. Martin Soloey Myrland is acknowledged for assistance in making tables. MB is supported by a NHMRC Senior Principal Research Fellowship and Leadership 3 Investigator grant (1156072 and 2017131).

**References**


