Letter to the Editor

Differences in eotaxin serum levels patients with recent onset and in chronic stable schizophrenia: A clue for understanding accelerating aging profile

Dear Editors,

A promising strategy to investigate the role of inflammation in schizophrenia (SZ) is to focus on a special type of cytokines involved in the attraction of cells to the inflammatory site, such as the chemokines CXCL-10/IP-10, CXCL-8/IL-8, CCL-11/Eotaxin, CCL-24/Eotaxin-2, CCL-2/MCP-1, and CCL-3/MIP-1 (Potvin et al., 2008; Miller et al., 2011). Evidence points towards an interaction between chemokine and neurotransmitter systems in the brain, playing crucial roles in brain development and function (Capuron and Miller, 2011). Beyond that, chemokines have been suggested as potentially useful biomarkers in psychiatric disorders such as SZ (Reale et al., 2011) commonly associated to accelerated biological aging (Porton et al., 2008). Increased CCL-11 serum levels together with impaired neurogenesis in hippocampus were seen in young mice after infusion of plasma from old mice (Villeda et al., 2011) Nevertheless, only few studies have evaluated the role of chemokines in the neurobiology of SZ (Teixeira et al., 2008; Reale et al., 2011).

Since understanding the role of trait disease biomarkers in SZ could potentially open new staging possibilities in order to personalize, optimize and improve treatments, the aim of this study was to investigate serum levels of two chemokines: CCL-11 (Eotaxin) and CCL-24 (Eotaxin-2), in recent onset (RO) and chronic patients (CP) with SZ in symptomatic remission.

Methods have been described elsewhere (Teixeira et al., 2008; Pedrini et al., 2012). Forty-two outpatients with SZ and thirty-seven healthy controls matched for age, gender, body mass index and level of education were recruited. The double case-control design included 23 RO patients (within first 5 years of SZ diagnosis), 19 CP (minimum of 20 years after the diagnosis of SZ) and their respective matched controls (19 and 18 subjects). Symptomatic remission was defined as BPRS scores below 15. All subjects had blood samples collected between 2 pm and 4 pm.

The subjects’ characteristics are summarized in Table 1. CCL-24 serum levels were significantly higher in RO (p = 0.010) and CP (p = 0.034) with SZ compared to controls. CCL-11 serum levels were not different in RO (p = 0.806) and increased in CP (p = 0.001) compared to controls. There was no significant correlation between age and CCL-11 in controls (p = 0.225; rho = −0.204) and all groups together (p = 0.225; rho = −0.204), and a correlation trend in patients (p = 0.081; rho = 0.303). There was a correlation trend between illness duration and CCL-11 levels (p = 0.093; rho = 0.293).

To our knowledge, this is the first study to examine serum chemokine levels in a sample of two groups of patients with SZ, differing in illness duration: 2.88 (1.86) years for RO and 25.61 (4.79) years for CP.

This study shows that CCL-11 and CCL-24 serum levels were increased in CP when compared to controls. Regarding RO patients, CCL-24 levels were also increased, but CCL-11 levels were not different from controls.

In a recent preclinical study, the infusion of plasma from old mice to young ones led to increased plasma levels of CCL-11 in the young mice (Villeda et al., 2011). Thus, Villeda’s study reached to the interesting, but yet speculative conclusion that this chemokine could be associated to hippocampus neurogenesis impairment and brain aging (Villeda et al., 2011). In addition, it has been shown that increased CCL-11 serum levels in individuals with SZ are inversely correlated to performance in working memory test (Asevedo et al., 2013). It has also been established that CCL-11 increases with age in both humans and rodents (Fernandez-Egea et al., 2013).

This study design was cross-sectional; it did not allow us a direct examination of the course of chemokines in SZ, only differences between controls and patients in different phases of SZ. The inclusion of two control groups matched to RO and chronic stage groups allowed differentiation of age, sex, body mass index and diagnosis effects. The effect of cigarette smoking on serum biomarkers could not be excluded, however there were no differences in number of cigarettes smoked a day between groups. Although the effect of medication could not also be excluded, it has been reported that antipsychotics would decrease central and peripheral inflammation (Miller et al., 2011).

Supporting the hypothesis that SZ is associated with a pro-inflammatory activation, this study importantly suggests that higher levels of serum peripheral CCL-11 are increased in patients with more than 20 years of disease compared to their controls, at least in this cohort; and might be a trait biomarker for accelerated aging process that occurs in SZ. This is probably related to a greater inflammatory activation, impaired functionality, increased mortality, and to other clinical diseases that overlap in patients with SZ. Additional studies relating telomere shortening with CCL-11 would be helpful in giving a sharper answer about the role of CCL-11 in SZ as a possible trait biomarker. Discovering this chemokine’s role and adopting a clinical staging model approach are particularly useful and may help to prevent the pathological aging consequences and optimize treatment strategies for this condition.

References


Table 1

Characteristics of healthy controls and patients with schizophrenia.

<table>
<thead>
<tr>
<th></th>
<th>Recent onset (RO)</th>
<th>Controls (n = 19)</th>
<th>p-Value</th>
<th>Chronic patients (CP)</th>
<th>Controls (n = 18)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (male/female)</td>
<td>13/10</td>
<td>10/9</td>
<td>0.523</td>
<td>15/4</td>
<td>13/5</td>
<td>0.714</td>
</tr>
<tr>
<td>Age in years</td>
<td>24.70 (4.78)</td>
<td>25.32 (5.19)</td>
<td>0.692</td>
<td>47.47 (3.41)</td>
<td>46.89 (4.28)</td>
<td>0.650</td>
</tr>
<tr>
<td>Years of education</td>
<td>11.32 (1.09)</td>
<td>11.32 (1.09)</td>
<td>0.112</td>
<td>10.26 (3.22)</td>
<td>10.39 (3.22)</td>
<td>0.906</td>
</tr>
<tr>
<td>Years of disease</td>
<td>2.52 (1.83)</td>
<td>–</td>
<td>–</td>
<td>25.63 (4.66)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Number of cigarettes a day</td>
<td>22</td>
<td>23</td>
<td>0.358</td>
<td>17</td>
<td>17</td>
<td>0.580</td>
</tr>
<tr>
<td>Less than 10</td>
<td>1</td>
<td>0</td>
<td>–</td>
<td>2</td>
<td>1</td>
<td>–</td>
</tr>
<tr>
<td>Antipsychotic daily dose, in mg of chlorpromazine equivalents</td>
<td>400 (194.24)</td>
<td>–</td>
<td>–</td>
<td>624 (203.01)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Body mass index</td>
<td>25.05 (5.19)</td>
<td>26.31 (5.17)</td>
<td>0.426</td>
<td>26.66 (2.64)</td>
<td>26.24 (5.46)</td>
<td>0.768</td>
</tr>
<tr>
<td>BPRS total scores</td>
<td>10 (4)</td>
<td>–</td>
<td>–</td>
<td>13 (9)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>CCL11</td>
<td>775.01 (1215.23)</td>
<td>837.04 (696.79)</td>
<td>0.806</td>
<td>1294.18 (2064.21)</td>
<td>614.59 (726.42)</td>
<td>0.001</td>
</tr>
<tr>
<td>CCL24</td>
<td>5440.03 (5081.67)</td>
<td>3668.58 (2952.29)</td>
<td>0.010</td>
<td>5382.73 (5367.92)</td>
<td>3087.88 (2947.88)</td>
<td>0.034</td>
</tr>
</tbody>
</table>

* Chi-square.
* Mean (standard deviation).
* T-test.
* Median (interquartile range).
* Mann-Whitney.


Natalia Pessoa Rocha
Interdisciplinary Laboratory of Medical Investigation, Faculdade de Medicina, Universidade Federal de Minas Gerais, Brazil

Mariana D. Curra
Laboratory of Molecular Psychiatry, INCT for Translational Medicine, Hospital de Clínicas de Porto Alegre, Universidade Federal do Rio Grande do Sul, Porto Alegre, Brazil

Bruna S. Panizzutti
Laboratory of Molecular Psychiatry, INCT for Translational Medicine, Hospital de Clínicas de Porto Alegre, Universidade Federal do Rio Grande do Sul, Porto Alegre, Brazil

Programa de Pós-Graduação em Medicina: Psiquiatria, Universidade Federal do Rio Grande do Sul, Porto Alegre, Brazil

Antonio L. Teixeira
Interdisciplinary Laboratory of Medical Investigation, Faculdade de Medicina, Universidade Federal de Minas Gerais, Brazil

Clarissa S. Gama
Laboratory of Molecular Psychiatry, INCT for Translational Medicine, Hospital de Clínicas de Porto Alegre, Universidade Federal do Rio Grande do Sul, Porto Alegre, Brazil

Programa de Pós-Graduação em Medicina: Psiquiatria, Universidade Federal do Rio Grande do Sul, Porto Alegre, Brazil

Corresponding author at: Hospital de Clínicas de Porto Alegre/CPE, Laboratory of Molecular Psychiatry, Rua Ramiro Barcelos, 2350, Prédio Anexo, 90035-903 Porto Alegre, RS, Brazil. Tel.: +55 51 33598845; fax: +55 51 33598846.

E-mail address: clarissasgama@gmail.com.

13 October 2013