PAI-1 AS A COMPONENT OF THE METABOLIC SYNDROME IN DEPRESSION AND SCHIZOPHRENIA – CROATIAN EXPERIENCE

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Mental stress affects coagulation, while severe mental illnesses, such as recurrent depression and schizophrenia, are associated with an increased thrombotic risk and cardiovascular morbidity. Evidence indicates that the hemostatic system is involved in the pathogenesis of morbidities and prognosis of a wide variety of psychiatric disorders (Hoirisch-Clapauch et al. 2014).

Clot buster tissue plasminogen activator (tPA) and its end-product plasmin play a well-defined role in neurochemistry. They mediate a number of events that culminate in tolerance against excitotoxicity, hippocampal neurogenesis, synaptic remodeling, neuronal plasticity, cognitive and emotional processing. Plasminogen-Activator Inhibitor Type 1 (PAI-1) provides an important mechanism for controlling the activity of t-PA. Abnormalities in these processes have been implicated in schizophrenia pathogenesis (Hoirisch-Clapauch & Nardi 2014).

The role of inflammation in major depressive disorder (MDD) may be explained as imbalance between pro-inflammatory mediators such as cytokines, chemokines and acute phase proteins and anti-inflammatory mediators. Cytokines have been found to influence almost every pathway involved in the pathogenesis of depression including alterations to the expression of neurotransmitters, neuroendocrine function, synaptic plasticity and basal ganglia (Patel 2013).

Plasma PAI-1 levels are increased in abdominally obese subjects and inflammatory states, such as depression and metabolic syndrome (MS), increasing the risk for intravascular thrombus occurrence and adverse cardiovascular outcomes. With obesity and progressive adipocytes enlargement, the blood supply to adipocytes may be reduced due to consequent hypoxia. Hypoxia has also been proposed to be an inciting etiology of necrosis and macrophage infiltration into adipose tissue that leads to an overproduction of biologically active metabolites known as adipocytokines which includes glycerol, free fatty acids (FFA), proinflammatory mediators (tumor necrosis factor alpha (TNFα) and interleukin-6 (IL-6)), PAI-1 and C-reactive protein (CRP). This results in a localized inflammation in adipose tissue that propagates an overall systemic inflammation associated with the development of obesity related comorbidities. Adipocytokines integrate the endocrine, autocrine, and paracrine signals to mediate the multiple processes including insulin sensitivity, oxidant stress, energy metabolism, blood coagulation, and inflammatory responses which are thought to accelerate atherosclerosis, plaque rupture, and atherothrombosis (Kaur 2014).

Metabolic syndrome is a state of chronic low grade inflammation as a consequence of complex interplay between genetic and environmental factors. Insulin resistance, visceral adiposity, atherogenic dyslipidemia, endothelial dysfunction, genetic susceptibility, elevated blood pressure, hypercoagulable state, and chronic stress are the several factors which constitute the syndrome (Kaur 2014).

Given the abovementioned clinical implications of metabolic syndrome in psychiatric patients, the aim of our study was to assess the presence of MS in patients with schizophrenia and recurrent depression, in comparison to a healthy control group. Furthermore, we investigated the relationship between MS and several inflammatory and coagulation factors among psychiatric patients (Lasić et al. 2014). The diagnosis of MS was defined according to the American National Institute of Health, Third Report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults criteria (NCEP ATP III), which require the presence of three or more of the following five criteria: 1) increased waist circumference: >88 cm in women or >102 cm in men; 2) elevated triglycerides: ≥1.7 mmol/L; 3) reduced highdensity lipoprotein (HDL) cholesterol: <1.03 mmol/L in men or <1.29 mmol/L in women; 4) elevated blood pressure: ≥130/85 mm/Hg; 5) elevated fasting glucose: ≥5.6 mmol/L. With the analyzer BCS „Siemens“ for coagulation tests the PAI-1 levels were determined. Diagnosis of the schizophrenia and MDD was determined from the Medical history and through a specialist psychiatric examination of each patient in accordance with ICD-10.

The patients with and without metabolic syndrome had different serum levels of PAI-1 regardless of their psychiatric diagnosis (depression or schizophrenia). Both group of patients exhibited higher levels of PAI-1 among those who also suffered from metabolic syndrome (Table 1).
Table 1. Comparison of markers of inflammation in cases with depression and schizophrenia, according to the presence of metabolic syndrome

<table>
<thead>
<tr>
<th></th>
<th>MS (n=19)</th>
<th>Depression without MS (n=26)</th>
<th>P</th>
<th>Schizophrenia</th>
<th>MS (n=21)</th>
<th>Schizophrenia without MS (n=23)</th>
<th>P</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>PAI-1</td>
<td>2.56±1.96</td>
<td>1.39±1.29</td>
<td>0.041</td>
<td>2.96±1.94</td>
<td>1.85±1.17</td>
<td>0.027</td>
<td>0.465</td>
<td>0.128</td>
<td></td>
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<tr>
<td>CRP</td>
<td>7.09±6.21</td>
<td>4.92±5.68</td>
<td>0.012</td>
<td>7.01±5.91</td>
<td>5.13±3.68</td>
<td>0.263</td>
<td>0.850</td>
<td>0.719</td>
<td></td>
</tr>
</tbody>
</table>

*The last two columns are comparisons of subgroups with and without MS, between cases with depression and schizophrenia*

Plasma levels of PAI-1 correlate positively with features of the metabolic syndrome. Depression is characterized by high PAI-1 levels, and conditions related to a hypofibrinolytic status, such metabolic syndrome, are associated with an increased risk for both depression and cardiovascular events (Hoirisch-Clapauch et al. 2013). We were the first researchers in Croatia who have investigated the role of the PAI-1 as the component of the MS in depression and schizophrenia, and our findings were consistent with those in the foreign literature.

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Conflict of interest: None to declare.

References

1. Hoirisch-Clapauch S, Nardi AE: Markers of low activity of tissue plasminogen activator/plasmin are prevalent in schizophrenia patients. Schizophr Res 2014; 159:118-23.