C-Reactive Protein associated to illness severity in schizophrenia

Paulo Belmonde-Abreu, Clarissa S Gama, Maria Inês Lobato, Raffael Massuda, Viviane Cristiano and Michele Paiva-Mendonça

Schizophrenia Program, Hospital de Clínicas de Porto Alegre Post-Graduation Program in Psychiatry Universidade Federal do Rio Grande do Sul - Brasil

Justification:
Recent evidence of increased inflammatory status and oxidative stress in schizophrenia, associated to two-fold increase of overweight, diabetes and hypertension and five-fold increase of dyslipidemia compared to the general population

Need to identify the weight of different factors, like inflammatory process, illness severity, illness progression, and exposure to neuroleptics, controlling to the effect of body weight and height, diet, physical activity and smoking

Method:
DSM-IVR Schizophrenia after 4 interviews with patient and family, clinically stable under regular visits and antipsychotics. Outpatient Program at Public Health System in a major teaching hospital (Hospital de Clínicas de Porto Alegre-HCPA). Patients collected blood samples (von Willebrand Factor and CRP (C-Reactive Protein), performed 6 min walking test, and rated for illness severity (#hospital admissions/year ill), BMI, smoking, relatives inquired about history of Infection during gestation (Project # 2011/0083).

Results:
N=40 (34 males, 6 females) signed informed consent approved by the ethic committee of HCPA

Increased illness severity; Linear Regression: VWF (p=0.365) cut-off p75 = 127.45
CRP (p=0.013) cut-off p75= 10.49

1. Linear Regression: decreased functional capacity among subjects with elevated PCR and increased illness severity (p=0.013).
2. CRP associated to illness severity (p=0.013)
3. VWF not associated to illness severity (p=0.365)
4. Effect remained after adjustment for smoking and BMI.
5. 10% of patients (4/40) reached the minimal expected walking distance, with a mean difference of 33% among men (p<0.05) and 18% among women (p>0.05)
6. Reduced functional capacity (reduced 6mWT) associated to increased CRP (p=0.029) and not with VWF (p=0.732) and smoking (p=0.502)
7. History of Infection during gestation associated to increased CRP (>4.0) (p=0.036)

Linear regression

<table>
<thead>
<tr>
<th>Model</th>
<th>Unstandardized Coefficient</th>
<th>Standardized Coefficient</th>
<th>t</th>
<th>Sig</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (Constant)</td>
<td>0.010</td>
<td>0.330</td>
<td>1.021</td>
<td>0.310</td>
</tr>
<tr>
<td>% smoking</td>
<td>0.004</td>
<td>0.003</td>
<td>-1.87</td>
<td>0.064</td>
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<td>BMI</td>
<td>0.019</td>
<td>0.011</td>
<td>0.038</td>
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<tr>
<td>MPO-oxidative</td>
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<td>0.001</td>
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<td>0.011</td>
<td>-1.17</td>
<td>0.251</td>
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<tr>
<td>% smoking</td>
<td>0.003</td>
<td>0.003</td>
<td>-1.17</td>
<td>0.251</td>
</tr>
<tr>
<td>BMI</td>
<td>0.019</td>
<td>0.011</td>
<td>0.036</td>
<td>0.769</td>
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<tr>
<td>MPO-oxidative</td>
<td>0.009</td>
<td>0.004</td>
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<tr>
<td>3 (Constant)</td>
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<td>0.011</td>
<td>0.216</td>
<td>0.830</td>
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<tr>
<td>% smoking</td>
<td>0.020</td>
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<td>0.830</td>
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<tr>
<td>BMI</td>
<td>0.024</td>
<td>0.004</td>
<td>0.408</td>
<td>0.682</td>
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</table>

Excluded Variables
- a. Predictors in the Model: (Constant), MPO-oxidative, %leth, BMI
- b. Predictors in the Model: (Constant), MPO-oxidative, BMI
- c. Dependent Variable: CRP = 10.49

Discussion:
- Increased pro-inflammatory pattern in schizophrenia
- Chronic systemic inflammation in SZ may explain the increase in metabolic abnormalities, such as diabetes mellitus, high blood pressure, obesity and dyslipidemia
- Evidence of association of inflammation and illness severity, controlling smoking, BMI and age.
- History of Infection in gestation associated to Increased CRP
- Limitations: CRP and not Ultra sensitive CRP (problems of low sensitivity, small sample size, large variability (std. deviation) Note: Need of larger samples with Ultra-sensitive assays

References
C-reactive protein associated to illness severity in schizophrenia

P. Belmonte-de-Abreu¹, C.S. Gama¹, M.I.R. Lobato², R. Massuda³, M. Pedrini², M. Fonseca³, V. Cristiano³
¹School of Medicine Federal University RS, Department of Psychiatry, Porto Alegre, Brazil
²Hospital de Clinicas de Porto Alegre, Service of Psychiatry, Porto Alegre, Brazil
³Programa de Pós-Graduação em Psiquiatria, Universidade Federal do Rio Grande do Sul, Porto Alegre, Brazil

Purpose of the study: The present study analyzed the association of C-Reactive Protein (CRP) and Von Willebrand Factor (VWF) with illness severity in stable outpatients with DSM-IV criteria of schizophrenia, based on previous studies of inflammatory status and oxidative stress in schizophrenia [1,2] and recent reviews [3], and controlling for several factors previously identified affecting inflammation and schizophrenia: (a) type of inflammatory process (cellular, endothelial), (b) illness severity, (c) illness course and progression, and (d) neuroleptic exposure. The measurement of these 4 factors addressed the gaps of previous studies focusing in cytokines and/or CRP, and most failed to address markers of endothelial dysfunction, like VWF, and very few controlled for the effect of BMI, smoking and physical activity and capacity.

Methods: Forty (34 males, 6 females) stable outpatient patients followed at the Schizophrenia Program in a major teaching hospital of Public Assistance (Hospital de Clinicas de Porto Alegre/HCPA) were enrolled after receiving full explanation of the study and signing informed consent approved by the ethic committee of HCPA (number 2011/0083). Patients collected blood samples for VWF and CRP analysis by standard commercially available tests at the Biochemistry Laboratory of the Hospital and performed the 6-minute walk test of functional capacity at the outpatient facilities under coordination by a Certified Physical Therapist.

Summary of results: It was identified that Increased illness severity (defined by the number of hospital admissions per year of illness) had strong association with CRP (r=0.442, p=0.004) but not with VWF, and Linear Regression revealed a trend to decreased functional capacity among subjects with elevated PCR and increased severity (p=0.064). CRP was associated to illness severity, whereas FVW not, and this effect remained after adjustment for tobacco use and BMI. Additionally, linear regression showed that subjects with higher CRP and increased illness severity tended to reduced functional capacity. All patients had lower functional performance by the walking test, with only 10% (4/40) reaching the minimal expected walking distance, with a mean difference of from the expected waling distance of 33% among men (p<0.05), and 18% among women (p>0.05) Smokers had lower functional capacity (0.051), and a strong tendency to display increased CRP (r=0.064).

Conclusions: The results confirms the evidence of increased inflammation in schizophrenia [3] and not through VWF pathway, and provides original evidence of association of inflammation and illness severity, even after controlling by drug use (clozapine X others), tobacco, BMI, functional capacity and age. This evidence of increased pro-inflammatory pattern reinforces their crucial role in neurodegeneration in schizophrenia. Chronic systemic inflammation in SZ may explain the increased morbidity (metabolic abnormalities, such as diabetes mellitus, high blood pressure, obesity and dyslipidemia) and mortality in schizophrenia. Additional studies with larger samples and with additional markers must be performed to disentangle the specific patterns of inflammation in schizophrenia.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Range</th>
<th>Mean</th>
<th>Standard deviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>21–53</td>
<td>36.40</td>
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<tr>
<td>Years ill</td>
<td>1–28</td>
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<td>Hospital admissions 0–25</td>
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<td>BMI</td>
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<td>27.0</td>
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<tr>
<td>VWF</td>
<td>20.5–186.9</td>
<td>107.05</td>
<td>34.900</td>
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<tr>
<td>CRP</td>
<td>4.0–28.7</td>
<td>6.18</td>
<td>05.41</td>
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</table>


Citation: Eur Neuropsychopharmacol. 2014;24(Suppl 2):S572

Keywords
Schizophrenia: clinical
Neurophysiology: clinical
New research