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High C-reactive protein levels are associated with depressive symptoms in schizophrenia

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ABSTRACT

Background: Depressive symptoms are frequently associated with schizophrenia symptoms. C - Reactive protein (CRP), a marker of chronic inflammation, had been found elevated in patients with schizophrenia and in patients with depressive symptoms. However, the association between CRP level and depressive symptoms has been poorly investigated in patients with schizophrenia. The only study conducted found an association between high CRP levels and antidepressant consumption, but not with depressive symptoms investigated with the Calgary Depression Rating Scale for Schizophrenia (CDSS).

Objectives: The aim of this study was to evaluate CRP levels and depressive symptoms in patients with schizophrenia, and to determine whether high CRP levels are associated with depressive symptoms and/or antidepressant consumption, independently of potential confounding factors, especially tobacco-smoking and metabolic syndrome.

Methods: Three hundred and seven patients with schizophrenia were enrolled in this study (mean age = 35.74 years, 69.1% male gender). Depressive symptoms was investigated with the CDSS. Patients were classified in two groups: normal CRP level (≤ 3.0 mg/L) and high CRP level (> 3.0 mg/L). Current medication was recorded.

Results: 124 subjects (40.4%) were classified in the high CRP level group. After adjusting for confounding factors, these patients were found to have higher CDSS scores than those with normal CRP levels in multivariate analyses (p = 0.035, OR = 1.067, 95% CI = 1.004–1.132). No significant association between CRP levels and antidepressants consumption was found.

Limitations: The size sample is relatively small. The cut-off point for high cardiovascular risk was used to define the two groups. CRP was the sole marker of inflammation in this study and was collected at only one time point. The design of this study is cross-sectional and there are no conclusions about the directionality of the association between depression and inflammation in schizophrenia.

Conclusion: This study found an association between high rates of CRP levels and depressive symptoms in patients with schizophrenia, but no association with antidepressant consumption. Further studies are needed to investigate the impact of inflammation in schizophrenia.

1. Introduction

Schizophrenia occurs in around approximately 1% of the population worldwide and around 0.6–0.8% in France (McGrath et al., 2008). It is a chronic disease characterized by psychotic symptoms, cognitive impairment and functional decline (Dickinson et al., 2004; Bruijnzeel and Tandon, 2011). Depressive symptoms are also frequently associated in schizophrenia (Tandon et al., 2009; Andrianarisoa et al., 2017). Prevalence rates of major depressive disorder (MDD) in schizophrenia range from 30% to 70% (Majadas et al., 2012; Peitl et al., 2016). Presence of depressive symptoms in patients with schizophrenia has been associated with overall worse outcomes, greater comorbidity, poorer quality of life (Andrianarisoa et al., 2017), work impairment, deterioration of psychosocial functioning, greater risk of relapse and increased risk of suicide (Tandon et al., 2009). Better understanding of the pathophysiology of depressive symptoms in schizophrenia is thus

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necessary.

The contribution of chronic inflammation to major mental disorders has received increased attention in the last decade (Fond et al., 2014). Among other inflammatory factors, C-reactive protein (CRP) is a non-specific marker that has the following two advantages: i) it is easily measured in blood samples, and ii) it provides a reliable marker of chronic inflammation. CRP was first extensively studied as a predictor of cardiovascular disease (Emerging Risk Factors Collaboration et al., 2010), which is one of the leading causes of early mortality in patients with schizophrenia (Mitchell et al., 2013). Moreover, CRP levels were found elevated in patients with schizophrenia (Miller et al., 2014) and in patients with MDD (Howren et al., 2009; Strawbridge et al., 2015; Valkanova et al., 2013). In schizophrenia patients, high CRP levels have been associated not only with cardiovascular risk but also with more psychotic symptoms (Fan et al., 2007), with greater cognitive impairment (Dickerson et al., 2007, 2012; Bulzacka et al., 2016), and with greater sensory processing impairment (Micoulaud-Franchi et al., 2015) than in patients with low CRP levels. In patients with MDD, high CRP levels are considered to be a useful biomarker for predicting the risk of major depressive episode (Duivis et al., 2013; Wium-Andersen et al., 2014), and have been associated with the persistence of depressive symptoms under treatment (Zalli et al., 2016) and with differential response rates to antidepressants (Uher et al., 2014). However, whereas CRP levels are known to be associated with MDD, their association with depressive symptoms in schizophrenia has received little attention. Fond et al. (2016) found an association between high CRP levels in schizophrenia and antidepressant consumption, but not with depressive symptoms investigated with the Calgary Depression Rating Scale for Schizophrenia (CDSS).

This study sought to evaluate CRP levels and the level of depressive symptoms investigated with the CDSS but also to determine the prevalence of high CRP levels, MDD and antidepressant consumption rates in a sample of patients with stable schizophrenia. We sought to determine whether high CRP levels are associated with depressive symptoms and/or antidepressant consumption in patients with schizophrenia, independently of potential confounding factors, especially tobacco-smoking and metabolic syndrome.

2. Methods

2.1. Study participants

The study evaluated all prospective patients attending daytime hospital hours in our university and psychiatric hospital over a period of 5 years from June 2010 to June 2015. The inclusion criteria were as follows: (1) age 18–85 years old, (2) diagnosis of schizophrenia according to the DSM-IV-TR criteria, (3) antipsychotic and possibly antidepressant or mood stabilizing agent medication stable for a minimum of 3 months, and (4) French as native language. The exclusion criteria were as follows: (1) diagnoses other than schizophrenia or MDD on axis 1 of the DSM-IV-TR, except for nicotine dependence, (2) major non-psychiatric disease, (3) mental retardation and (4) any identifiable acute, intermittent or chronic infection or being on routine anti-inflammatory or immunosuppressive therapy. Acute and intermittent inflammations and infections have been excluded by a complete medical examination realized by a medical professional who investigate the body of the patient for symptoms and signs for disease, and in particular inflammation and infection diseases. Moreover, serologies were conducted for the following chronic infections: Human Immunodeficiency Virus, Hepatitis B Virus and Hepatitis C Virus. The data collection was approved by the *Commission Nationale de l'Informatique et des Libertés* (CNIL number 1223715). The study was designed in accordance with the Declaration of Helsinki and French good clinical practice. All of the patients were informed of the study and gave written informed consent.

2.2. Data collection

1. Socio-demographic information: gender, age, educational level
2. Clinical characteristics: duration of illness and age at illness onset, body mass index (BMI), tobacco, cannabis and alcohol consumption, psychotic symptoms based on the Positive and Negative Syndrome Scale (PANSS), with five factors (negative, positive, excited, depressive, cognitive) (Kay et al., 1986; Lançon et al., 2000), current depressive symptoms based on the Calgary Depression Rating Scale for Schizophrenia (CDSS) (Addington et al., 1993). The CDSS was specifically designed to identify specific depressive symptomatology that cannot be related to negative symptoms of schizophrenia. Depression is defined as scores above 6 (current "major depressive disorder" (MDD)), with a sensitivity of 88.9% and a specificity of 75% (Reine et al., 2000; Lançon et al., 1999).
3. Drug information: antipsychotic medication and chlorpromazine equivalent dose (in milligrams per day), use of antidepressants and mood stabilizing agents, used antipsychotic types and antidepressant classes.
4. Chronic inflammation marker: serum CRP levels were determined using sensitive regular immunoassays (ELISA). The results were expressed as milligrams per liter. The detection limit was 0.08 µg/ml. Patients were classified in two groups: normal CRP level ($\leq$ 3.0 mg/L) and high CRP level ($>$ 3.0 mg/L) (Wysokiński et al., 2014; Emerging Risk Factors Collaboration et al., 2010).
5. Metabolic Syndrome: diagnosis of metabolic syndrome was made according to the National Cholesterol Education Program ATP-III criteria (Grundy, 2005), including three or more of the following criteria: waist circumference $>$ 88 cm in women and $>$ 102 cm in men; fasting serum triglycerides $\geq$ 1.69 mmol/L; serum HDL $<$ 1.3 mmol/L in women and $<$ 1.0 mmol/L in men; blood pressure $\geq$ 190/85 mmHg; and fasting blood glucose levels $\geq$ 5.6 mmol/L. Waist circumference was measured at the midpoint between the lower rib margins and the iliac crest. Arterial blood pressure was recorded using a standard mercury sphygmomanometer. Glucose and lipoprotein concentrations were analyzed in fasting venous blood samples using standard enzymatic techniques.
6. Abdominal obesity was defined by the presence of both hypertriglyceridemia ($\geq$ 1.7 mmol/L) and high waist circumference ($>$ 94 cm for men and $>$ 80 cm for women) (Després and Lemieux, 2006).

2.3. Statistical analysis

Socio-demographics, clinical characteristics and comorbidities were presented using measures of means and dispersion (standard deviation) for continuous data and frequency distribution for categorical variables. Univariate associations between demographic and clinical characteristics of patients with high CRP levels were performed using the chi-square test for categorical variables and the Student *t*-test for continuous variables.

To explore the relationship between CRP level and depressive symptoms (CDSS score) in schizophrenia, we used a multivariate logistic regression model adjusting for potential confounders: age, gender, current tobacco consumption, use of antidepressants, presence of metabolic syndrome, and psychotic symptomatology (PANSS total score).

All the tests were two-sided. Statistical significance was defined as $p < 0.05$. Statistical analysis was performed using the SPSS version 18.0 software package (SPSS Inc., Chicago, IL, USA).

3. Results

3.1. Patient characteristics

Three hundred and seven patients with schizophrenia participated