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Increased serum interleukin-6 levels in early stages of psychosis: Associations with at-risk mental states and the severity of psychotic symptoms

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Summary Schizophrenia patients experience activated inflammatory responses, but little is known about the presence of such inflammatory processes at or prior to disease onset. We measured interleukin-6 (IL-6) and C-reactive protein (CRP) serum levels and plasma fibrinogen in 17 at-risk mental state (ARMS) subjects, 77 patients with psychotic disorder (PD) and 25 healthy control subjects (HC). ARMS subjects were followed-up, and transition to psychosis was registered. IL6 rs1800795 SNP was genotyped, as IL-6 levels may be influenced by this genetic variant. We did not observe significant differences in the IL6 rs1800795 SNP genotype frequencies between the groups. ARMS subjects exhibited significantly higher IL-6 levels than did controls ($p = 0.019$). In subjects not taking cannabis, we found that patients diagnosed with ARMS or PD exhibited increased IL-6 levels when compared with HC ($p = 0.004$). In both ARMS and PD subjects, IL-6 levels were positively associated with negative symptoms. However, with respect to positive psychotic symptoms, a different relationship was observed in the ARMS and PD groups (positive relationship in ARMS; negative relationship in PD). These findings could not be attributed to confounding variables, including gender, body mass index (BMI), tobacco consumption or the rs1800795 genotype. Six of 17 ARMS subjects (35%) exhibited a transition to psychosis during the follow-up period of 26 months. ARMS subjects who developed psychosis exhibited increased median IL-6 levels compared with those who did not transition (0.61 vs. 0.35 pg/mL). However, this difference was not statistically significant, which could be explained by a lack of statistical power due to the small sample size. Our results suggest that IL-6 may be a biomarker for early psychotic symptoms; however, further studies in larger samples are needed to confirm this result.

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1. Introduction

Schizophrenia is a complex multidimensional syndrome characterized by positive symptoms (e.g., delusions, hallucinations), negative symptoms (e.g., motivational impairment), affective dysregulation (e.g., depression, mania or anxiety) and cognitive alterations (van Os et al., 2010). Despite past research efforts that have attempted to identify psychological, biological and environmental risk factors, the precise causes of schizophrenia are not well-known. Inflammation may play a role in the pathogenesis of psychoses, based on the presence of immunological anomalies in schizophrenia that include activated innate and acquired immune response cells (Smith, 1992), and in the consequent elevations of specific cytokines and inflammatory mediators such as IL-6 and CRP (Fan et al., 2007; Potvin et al., 2008; Miller et al., 2011, 2013).

IL-6 is a pleiotropic cytokine synthesized by activated monocytes and Th2 lymphocytes (Muller et al., 2000). It induces acute-phase proteins and promotes differentiation of B cells into antibody-producing plasmatic cells (Kishimoto, 2010). In a recent meta-analysis that explored the association between acute exacerbations of schizophrenia and immune system dysfunction, IL-6 was significantly increased in 5 of 6 studies of acutely relapsed inpatients and in 4 of 4 studies of patients experiencing their first psychotic episodes compared with healthy controls (Miller et al., 2011).

Previous studies have suggested that IL-6 levels may be influenced by genetic variants in the human IL-6 gene (IL6) (Fishman et al., 1998). IL6 is located on the short arm of chromosome 7. The functional IL6 single nucleotide polymorphism (SNP) rs1800795 consists of a G to C change at position −174 in the promoter region. Allele C has been associated with a reduced expression of IL6, in comparison with allele G (Fishman et al., 1998). Previous studies conducted with Polish and Armenian schizophrenia patients have shown inconsistent results in terms of allele frequencies, genotype frequencies and associations between genotype and IL-6 levels (Zakharyan et al., 2012; Paul-Samojedny et al., 2013). In syndromes or diseases in which inflammation plays an important pathophysiological role (e.g., insulin resistance, type-2 diabetes mellitus, and systemic-onset juvenile chronic arthritis), researchers have identified associations between IL-6 serum levels and the IL6 promoter SNP rs1800795 (Cardellini et al., 2005; Fishman et al., 1998; Vozarova et al., 2003). Recently, an association has also been identified between the rs1800795 genotype and interferon alpha-induced neuropsychiatric symptoms in subjects with chronic hepatitis C (Udina et al., 2013).

CRP and fibrinogen are acute-phase proteins synthesized in the liver by direct stimulation of IL-6. Both can serve as non-specific markers of infection and chronic inflammation (Pfafflin and Schleicher, 2009). Fibrinogen also is an important element in the coagulation cascade (Levy et al., 2012). Elevated serum CRP and plasma fibrinogen levels have been reported in schizophrenia patients when compared with healthy controls (Maes et al., 1997; Garcia-Rizo et al., 2012).

A few studies have explored the relationship between the clinical expression of schizophrenia and inflammatory markers. Elevated CRP levels have been found to be associated with more severe clinical symptoms measured by the total, negative and general scales of the PANSS (Fan et al., 2007) and lower cognitive functioning in patients with schizophrenia (Dickerson et al., 2007). Higher serum IL-6 levels have been associated with a longer duration of the illness (Ganguli et al., 1994) and a poor clinical profile characterized by resistance to antipsychotic pharmacotherapy (Lin et al., 1998). The above-mentioned correlations could possibly indicate a relationship between a marked inflammatory process and more severe psychopathology in a subgroup of patients with schizophrenia.

Most studies exploring the role of inflammatory markers in psychosis have been conducted on subjects with long durations of illness, and only a few studies suggest that inflammatory abnormalities are present in newly diagnosed antipsychotic-naïve patients (Borovcanin et al., 2012; Garcia-Rizo et al., 2012). To date, no studies have explored whether increased inflammatory factors are present in patients who are at risk of psychosis, nor have any investigated the influence of the IL6 rs1800795 SNP genotype on IL-6 levels in early-psychosis patients. The ARMS is a clinical construct that attempts to identify individuals with prodromal symptoms of psychosis. Thirty percent of ARMS subjects will develop psychosis at one year after diagnosis (Fusar-Poli et al., 2013). Although ARMS individuals often receive early intervention services, the clinical utility of the diagnosis has been a controversial issue. Interestingly, an attenuated psychosis syndrome has recently been included in Section III of the DSM-V, along with conditions that require further study.

Thus, we hypothesized that ARMS subjects and individuals with a psychotic disorder at early stages of illness would show increased inflammatory markers when compared to healthy controls (HC). Additionally, we hypothesized that inflammation would be associated with the phenotypical expression of the illness (i.e., the severity of positive and negative symptoms).

Finally, as previous association studies of rs1800795 and schizophrenia have produced inconclusive results, we aimed to conduct a case-control association study with a group of early psychosis patients. Furthermore, considering the known influence of rs1800795 SNP on IL6 expression, we hypothesized that rs1800795 could be a risk factor for early psychotic symptoms and could potentially predict the elevations in IL-6 serum levels in the early stages of schizophrenia.

2. Methods

2.1. Participants

We selected 94 male and female patients (18—35 years of age) attending our Early Psychosis Program (HUIPM, Reus, Spain) and 25 healthy individuals. Patients were classified into 2 groups: 17 ARMS subjects with prodromal psychotic symptoms and 77 patients with psychotic disorder (PD) whose durations of illness were less than 5 years. The DSM-IV diagnoses for PD were as follows: schizophreniform disorder ($n = 19$), schizophrenia ($n = 12$), schizoaffective disorder ($n = 10$), and psychotic disorder not otherwise specified ($n = 36$). Patients diagnosed with substance-induced psychosis, neurological disorders or mental retardation were excluded. The group of healthy control subjects (HC, $n = 25$) was screened to rule out past or current histories of psychiatric disorders. Recruitment of HC included