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Antipsychotic treatment reduces psychotic symptoms and markers of low-grade inflammation in first episode psychosis patients, but increases their body mass index

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ABSTRACT

Objective: The main goal of the present study was to analyze levels of cytokines of the interleukin family (IL-1α, IL-1β, IL-2, IL-4, IL-6, IL-8 and IL-10), interferon-gamma (IFN-γ), monocyte chemoattractant protein-1 (MCP1), tumor necrosis factor-alpha (TNF-α), and vascular endothelial and endothelial growth factors (VEGF and EGF), in the blood samples of first-episode psychosis (FEP) patients before and seven months after the start of antipsychotic medication use.
Method: 38 anti-psychotic medication-naïve FEP patients and 37 healthy controls (HC) were recruited. Biochip array technology was used to measure cytokines and growth factors.
Results: The comparison of these markers in FEP patients and HC revealed significantly higher levels of EGF, IL-4 and IL-6 and significantly lower level of IL-1β in FEP patients before the antipsychotic treatment. Multiple regression analysis demonstrated significant correlations between FEP and EGF, IL-1β and smoking. Treatment with antipsychotic drugs resulted in a statistically significant amelioration of the symptoms of psychosis, but caused a significant increase in the body mass index (BMI) of patients. Levels of EGF, IL-2, VEGF, IL-6, IFN-γ, IL-4, IL-8 and IL-1α were significantly lower in treated FEP patients compared to premedication levels.
Conclusions: According to the present study, EGF and IL-1β are markers of FEP. Antipsychotic drug treatment resulted in a significant clinical improvement of FEP patients and the suppression of positive symptoms was correlated with the decreased levels of EGF, IL-2 and IL-4. EGF was the strongest marker of FEP and treatment efficiency among the measured cytokines and growth factors.

1. Introduction

There is a growing interest in studying the prodromal stage of schizophrenia, as well as first episode development of the disease (Malla et al., 2002). However, the underlying pathological alterations that are thought to occur during the early stages of schizophrenia remain to be established. The vast majority of biological research on schizophrenia has addressed neurotransmitter abnormalities (Aghajanian and Marek, 2000; Jones et al., 2005), genetic predisposition (Craddock et al., 2005), viral infections (Bradbury and Miller, 1985) and obstetric complications (Clarke et al., 2006). Increasing evidence also suggests that altered immunological regulation plays a role in the development of schizophrenia. Pathogenetic mechanisms that result from schizophrenia have been associated with abnormal activation of the immune system (Muller and Schwarz, 2007, 2010; Miller et al., 2011). Immune alterations can be found within the brain and cerebrospinal fluid, as well as in the blood serum and leukocytes of schizophrenia patients (Maino et al., 2007; Potvin et al., 2008; Chan et al., 2011; Drexhage et al., 2011a, 2011b; Miller et al., 2011; Schwarz et al., 2012). These findings suggest that systemic inflammatory alterations occur in schizophrenic patients.

Miller et al. (2011) conducted a meta-analysis of 40 studies about the impact of cytokines upon first-episode psychosis (FEP). By comparing FEP patients with acutely relapsed psychotic inpatients and HC, it was found that alterations of cytokines were similar for studies of acutely relapsed and FEP patients. Interleukin (IL)-1β and IL-6, and the transforming growth factor-β (TGF-β), appeared to be psychotic state markers, as they increased in both groups of patients and normalized with antipsychotic treatment. IL-2, interferon-gamma (IFN-γ), tumor necrosis factor-alpha (TNF-α) and soluble IL-2 receptors (sIL-2r)

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appeared to be trait markers, because their levels were elevated during acute exacerbations and remained so following antipsychotic treatment. Miller et al. (2011) suggest that although these results could provide a basis for future analysis, most studies did not control for potentially confounding factors such as body mass index (BMI) or smoking.

Upthegrove et al. (2014) recently conducted another meta-analysis of FEP. Papers that contained sufficiently stratified cytokine data were included in a random-effects pooled effect size meta-analysis. 23 studies reporting data on 570 patients, 683 healthy subjects, and 20 cytokines/cytokine receptors, were included. Highly significant effects were found for elevated IL-1β, sIL-2r, IL-6 and TNF-α. Non-significant effects were obtained for IL-2, IL-4 and IFN-γ. Although the results of this meta-analysis differed to some extent from that of Miller et al. (2011), they confirmed the major findings of the first meta-analysis in that pro-inflammatory cytokine levels were elevated in the serum samples of antipsychotic medication-naïve FEP patients.

Most studies have not yielded conclusive results owing to limitations of sample size, dissimilarities in the clinical status of patients, and the variability of cytokine levels within the general population (De Witte et al., 2014). De Witte et al. (2014) attempted to account for these limitations by carrying out standardized analyses of 9 cytokines in the serum of 180 antipsychotic medication-naïve FEP patients and 350 matched controls across 5 different clinical cohorts. All subjects were matched for potentially confounding factors, including age, gender, smoking and BMI. They found that levels of the IL-1 receptor antagonist (IL-1RA) and IL-10 and IL-15 increased significantly in patients across all cohorts. Moreover, levels of IL-1RA and IL-10 decreased in 32 patients who had been treated for 6 weeks with atypical antipsychotics. However, Xiu et al. (2014) found antipsychotic medication-naïve FEP patients exhibited significant decreases in IL-10 levels compared to HC. For patients' serum, IL-10 was negatively correlated with Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987) negative symptom scores and cognitive factor sub-scores. Xiu et al. (2014) suggest that low IL-10 may result in the negative symptoms and cognitive impairment during acute schizophrenia episodes. However, as this study was limited to the Chinese Han population, the authors note that their findings would be significantly strengthened if they were replicated for a set of samples from a different ancestry (e.g. Caucasian).

Altogether the existing data concerning antipsychotic medication-naïve FEP patients remains controversial. Nevertheless, there is considerable evidence to suggest that low-grade inflammation already occurs during the early stages of schizophrenia manifestation (Miller et al., 2011; De Witte et al., 2014; Upthegrove et al., 2014).

1.1. Aims of the study

The goal of the present study was to build up current knowledge by analyzing low-grade inflammation status contribute to the aforementioned studies using a sample of FEP patients and selected HC from the catchment area of Tartu University Hospital, Estonia. We attempted to control for different confounding factors (e.g. BMI and smoking status) and focused on a wide range of inflammatory markers, including pro-inflammatory cytokines (IL-1α, IL-1β, IL-2, IL-6, IFN-γ and TNF-α), anti-inflammatory cytokines (IL-4 and IL-10), chemokines (IL-8 and monocyte chemoattractant protein-1 (MCP-1)), and vascular endothelial and endothelial growth factors (VEGF and EGF), in order to capture a comprehensive picture of inflammatory patterns in FEP patients.

The first aim of this study was to investigate differences in serum inflammatory markers between antipsychotic medication-naïve FEP subjects and HC. The second aim was to evaluate the effect of antipsychotic medication on the clinical symptoms, BMI, and levels of cytokines and growth factors of the FEP patients approximately seven months after first treatment.

2. Material and methods

2.1. Participants

38 FEP patients were recruited from the Psychiatric Clinic of Tartu University Hospital, Estonia (Table 1). The patients fulfilled the following inclusion criteria: were aged between 18 and 45; had experienced a first psychotic episode; the duration of their untreated psychosis had been less than 3 years; no antipsychotic treatment received before the first contact with medical services for psychosis. Patients were excluded from the study if they had psychotic disorders owing to a general medical condition or had substance induced psychosis. FEP diagnoses were based on clinical interviews according to the International Classification of Diseases, Tenth Edition (ICD-10) (World Health Organization, 1992) criteria. 36 FEP patients underwent treatment using antipsychotic medication (two refused) and were included in the follow-up analysis. History of antipsychotic medication use was collected according to reviews of patients' medical charts. Patients were treated with various antipsychotic medications according to what was clinically indicated (Table 2). During the follow-up period, patients received either atypical ($n = 24$), typical ($n = 1$) or mixed ($n = 11$) antipsychotic medication; the mean theoretical chlorpromazine dose equivalent (Gardner et al., 2010) was 396 ± 154 mg (range 80–640). 28 patients were treated only with antipsychotics, but 5 patients additionally needed mood stabilizers and 6 patients also received antidepressants or hypnotics.

37 mentally healthy subjects participated in the study as HC. The HC sample was recruited by advertising in the same geographical area the FEP patients came from. Both patients and HC were interviewed by experienced psychiatric doctors in order to avoid the inclusion as controls of subjects with mental disorders. Exclusion criteria for the control group also included psychotic disorders among close relatives. As it was a naturalistic study, cigarette smoking and substance abuse were not exclusion criteria for either group. Using the information obtained from the participants, we determined that 8 patients (21.1%, all men) and 7 healthy controls (18.9%, three of which were men) were current cigarette smokers. In addition, 10 patients (including all the cigarette smokers) and one control (also a cigarette smoker) had used cannabis during their lifetime. Participants were enrolled between September 2009 and December 2013. The general demographic data for HC and FEP patients is listed in Table 1. The study was approved by the Ethics Committee of the University of Tartu, Estonia. Written informed consent was also obtained from all participants.

2.2. Procedure

For the FEP patients, blood samples and clinical and BMI data were assessed at two time points: on admission and after the follow-up period (mean duration 7.18 ± 0.73 months). Symptom severity was measured using PANSS (Kay et al., 1987), a rating instrument that evaluates the presence and severity of positive, negative and general

Table 1
Group size, age, BMI and smoking in study groups: healthy controls (HC) and antipsychotic medication-naïve first-episode psychosis (FEP) patients.

	HC	FEP
Group size, n	37 (male 16, female 21)	38 (male 21, female 17)
Age (mean, SD, range)	24.8 ± 0.86 (18–39)	25.4 ± 0.89 (18–40)
Male	23.7 ± 1.15 (19–37)	25.1 ± 1.19 (19–40)
Female	25.7 ± 1.23 (18–39)	25.8 ± 1.40 (18–40)
BMI (mean, SD, range)	23.0 ± 0.50 (16.5–30.2)	22.5 ± 0.48 (18.4–30.2)
Male	24.0 ± 0.87 (18.4–30.2)	22.6 ± 0.72 (18.4–30.2)
Female	22.3 ± 0.55 (16.5–28.9)	22.5 ± 0.62 (18.4–27.6)
Smoking (M/F)	7 (3/4)	8 (8/0)

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