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Interleukin 1 receptor antagonist and soluble tumor necrosis factor receptor 1 are associated with general severity and psychotic symptoms in schizophrenia and bipolar disorder

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ABSTRACT

Background: Previous studies suggest elevated inflammation in schizophrenia and bipolar disorder, with increased activity of the Interleukin 1 (IL-1), interleukin 6 (IL-6), tumor necrosis factor (TNF)-alpha, von Willebrand factor (vWf) and osteoprotegerin (OPG). It is unclear how immune activation is involved in the psychopathology. We investigated if elevated inflammation was associated with disease severity (trait) or current symptom level (state), comparing psychotic with general characteristics.
Methods: Plasma levels of sTNF receptor 1 (sTNF-R1), IL-1 receptor antagonist (IL-1Ra), IL-6, vWf and OPG were measured with ELISA techniques in 322 patients with schizophrenia spectrum and bipolar disorder. Current symptom level (state) was measured with Global Assessment of Functioning (GAF) and Positive and Negative Syndrome Scale (PANSS). Disease severity (trait) was measured with premorbid adjustment scale (PAS), age at onset, number of psychotic episodes and number and length of hospitalizations.
Results: After controlling for confounders, IL-1Ra and TNF-R1 were independently associated with GAF, and significantly correlated with PANSS negative and positive, respectively. In addition, Il-1Ra was associated with PAS, and sTNF-R1 with number of hospitalizations and psychotic episodes. VWf was significantly correlated with psychotic episodes, OPG with hospitalizations and IL-6 with history of psychosis. Linear regression analysis showed that GAF remained associated with sTNF-R1 and IL-1Ra with PANSS, after controlling for the other clinical measures.
Conclusions: This supports that inflammatory markers, particularly IL-1Ra and sTNF-R1 are associated with both general disease severity and psychotic features. This supports a role of immune activation in the core pathological mechanisms of severe mental disorders.

1. Introduction

The underlying pathological mechanisms of severe mental disorders are still largely unknown. The disorders are highly heritable (Harrison and Weinberger, 2005) with complex genetic and environmental interactions involved (Burmeister et al., 2008). However, the specific mechanisms involved remain elusive. Several lines of evidence have implicated the immune system in the development of severe psychiatric disorders (Watanabe et al., 2010) and inflammatory mediators are involved in neurotransmission and cognition (McAfoose, 2009).

Psychotic features are common to both schizophrenia and bipolar disorder, although not all bipolar disorder patients have psychotic episodes (Jabben et al., 2009). Schizophrenia and bipolar disorder also have similarities in genetic risk factors, which support the hypotheses of a continuum (Williams et al., 2011). Several studies have reported signs of systemic inflammatory activation in both schizophrenia and bipolar disorder (Drexhage et al., 2011), although there has been many inconsistent results(Schmitt et al., 2005; Freudenreich et al., 2010; Kunz et al., 2011; Miller et al., 2011). According to a meta-analysis there is fairly consistent evidence of raised activity in three inflammatory pathways, the tumor necrosis factor (TNF), interleukin 1 (IL-1), and IL-6 (Drexhage et al., 2010). We previously reported a significant increase in sTNF receptor type 1 (sTNF-R1) and von Willebrand factor (vWf) (Hope et al., 2009). The patients also had

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increased levels of osteoprotegerin (OPG), a soluble decoy receptor in the TNF receptor superfamily related to calcium metabolism (Hope et al., 2010). There was no significant elevation of IL-6 or IL-1Ra, but these markers were associated with affective state and severity of depression in bipolar disorder (Hope et al., 2011).

Research into the relationship between immune factors and disorder characteristics in psychotic patient populations is sparse (Goldstein et al., 2009; Miller et al., 2011). To the best of our knowledge, there is no adequately powered study of associations between inflammatory markers and disorder severity across schizophrenia and bipolar disorder groups. Based on raised serum levels of sTNF, IL-β and IL-6 in previous meta-analysis, and our findings of elevated OPG and vWf in schizophrenia and bipolar disorders, we examined if activities in these pathways were associated with severity of the mental disorders. High cytokine levels may be a trait influenced by genetic factors (Rafiq et al., 2007; Clerici et al., 2009; Vistoropsky et al., 2010), and thus influence stable disease characteristics. In addition, cytokine levels may be affected by acute physical and mental challenges, and thus fluctuate in relation to stressors (Kop et al., 2008; Brydon et al., 2009). A cross-sectional study with no direct follow-up of disease characteristics related to fluctuations of immune markers in the individual has clear limitations concerning inferences about causality or direction of effect, but can provide valuable descriptive information. We investigated if inflammatory markers are associated with severity of psychotic disorders in an adequately powered study across both schizophrenia and bipolar disorder groups in the same sample of patients as in our previous studies (Hope et al., 2009, 2010). The hypothesis was that high levels of inflammation would be associated with more severe clinical symptom levels (*state*) and with a more severe disease history (*traits*).

2. Methods

2.1. Participants

The study population has previously been reported in detail (Hope et al., 2009). Briefly, patients were included through referrals to the ongoing Thematically Organized Psychosis (TOP) Study in Oslo, Norway (for details, see Birkenaes et al., 2007).

Inclusion criteria: being registered in the psychiatric services of any one of the four University Hospitals in Oslo; age 18 to 65 years; meeting DSM-IV criteria for schizophrenia or bipolar spectrum disorders.

Exclusion criteria: history of moderate or severe head injury, neurological disorder, mental retardation, malignancies and acute or chronic infectious disorders. The patients were included between 2003 and 2008. We do not have a precise number of all eligible patients, but the fraction of eligible patients that declined to participate or were not included for other reasons was 13%. Due to IRB regulations we could not collect information from the patients who declined to participate. However, previous analysis based on hospital charts from all treated psychotic patients found no significant difference between the study sample and the clinical hospital sample regarding illness severity and sociodemographic variables and substance abuse (Ringen et al., 2008). Included in the current analyses were consecutive referred patients with valid measurements of inflammatory markers, without any use of immunomodulating drugs including non-steroid anti-inflammatory drugs or statins, consisting of a total of 322 patients (192 had a DSM-IV non affective psychotic disorder, comprising schizophrenia [n = 147], schizophreniform [n = 11] and schizoaffective disorder [n = 34], 130 had a bipolar spectrum disorder (Bipolar I disorder [n = 77], Bipolar II disorder [n = 45] and Bipolar not otherwise specified [n = 8]). One patient had missing data regarding IL-1Ra and OPG. All participants gave written informed consent to participation including the permission to re-use the data for further analysis, and the study has been approved by the Regional Committee for Medical Research Ethics and the Norwegian Data Inspectorate.

2.2. Study design

We explored if markers of inflammation were associated with the current *clinical* severity (*state*) or history of disease severity (*trait*) of both *general* and *psychotic* characteristics in a cross-sectional study. We used Global Assessment of Functioning; (GAF) (Greenberg and Rosenheck, 2005; Aas, 2010) as measure of *general state*, and Positive and Negative Syndrome Scale; (PANSS) (Santor et al., 2007) as measure of *psychotic state*. *General traits* was measured with premorbid adjustment scale (PAS) (Brill et al., 2008), age at onset of first episode and number and length of hospitalizations and *psychotic traits* with history of psychosis, age at first psychotic episode and number of psychotic episodes.

2.2.1. Confounding factors

We included age, gender, ethnicity, smoking, alcohol intake, kidney and liver function, having a diagnosis of autoimmune disorder, hypertension, high-sensitivity C-reactive protein (hsCRP), medication with antipsychotics, mood stabilizers and antidepressants as confounders.

2.3. Assessments

All patients were assessed by trained clinical research personnel (psychiatrists and clinical psychologists). The Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I) was used for diagnostic purposes, and global symptomatology and functioning was measured by the GAF Scale (split version). Inter-rater reliability was good, with an overall kappa score of 0.77 (95% confidence interval: 0.60–0.94) for diagnoses and an ICC (1.1) of 0.86 for both symptom and function GAF scores, and 0.73, 0.73 and 0.71 for PANSS positive, negative and general subscales respectively. PANSS is a commonly used scale to measure symptoms in psychotic disorders (Kay et al., 1987). For all participants, daily smoking, the use of alcohol and drugs during the last 2 weeks prior to assessment was recorded.

2.4. Biochemical and Immunological measures

Blood sampling was performed between 8 am and 14 pm. The analysis of clinical chemistry parameters was performed at Department of Clinical Chemistry, Oslo University Hospital, Oslo, Norway on an Integra 800 from Roche Diagnostics (Basel, Switzerland) using standard methods. For immunological analysis, blood was drawn on EDTA vials, and plasma was extracted the next workday and stored at −80 °C. The methods for the measurements of plasma levels of sTNF-R1, IL-1Ra, OPG, vWf and hsCRP as well as the results from these measurements in the present study population have previously been reported (Hope et al., 2009, 2010), using enzyme immunoassays (EIA) obtained from R&D Systems, Minneapolis, MN (sTNFR1, IL-1Ra, OPG) or an EIA using antibodies from DakoCytomation (Oslo, Norway; vWf) (Bollerslev et al., 2006). In the vWf analyses, levels are given in plasma concentration percent (%) and the standard curve is based on samples from a plasma pool of healthy individuals, where the normal range is set to 70–130%. All intra- and inter-assay coefficients of variance were <10%.

2.5. Statistical procedures

All statistical analyses were done using the SPSS software package for Windows version 15.0 (SPSS, Chicago, IL). Bipolar disorder and schizophrenia were merged for the main analysis, and sub analyses were done for schizophrenia spectrum and bipolar disorder independently. All tests were two-sided with a preset level of significance of 0.05. Correlation tests were done by both Spearman's Rho and Pearson's dependent on the distribution of data. Regarding IL-1Ra, there were significant associations with both methods, and we reported the Pearson correlations, as these associations tended to be