Schizophrenia Research xxx (2014) xxx–xxx

Contents lists available at ScienceDirect

Schizophrenia Research

journal homepage: www.elsevier.com/locate/schres

Association between altered brain morphology and elevated peripheral endothelial markers — Implications for psychotic disorders

Ingrid Dieset [a,*], Unn Kristin Haukvik [a,b], Ingrid Melle [a], Jan Ivar Røssberg [a], Thor Ueland [c], Sigrun Hope [a], Anders M. Dale [f,g,h], Srdjan Djurovic [a,e], Pål Aukrust [c,d], Ingrid Agartz [a,b], Ole A. Andreassen [a]

[a] KG Jebsen Centre for Psychosis Research, Division of Mental Health and Addiction, Oslo University Hospital and Institute of Clinical Medicine, University of Oslo, Oslo, Norway
[b] Department of Psychiatric Research, Diakonhjemmet Hospital, Oslo, Norway
[c] Research Institute of Internal Medicine, Oslo University Hospital Rikshospitalet, Faculty of Medicine, University of Oslo, Oslo, Norway
[d] Section of Clinical Immunology and Infectious Diseases, Oslo University Hospital Rikshospitalet, Norway
[e] Department of Medical Genetics, Oslo University Hospital Ullevål, Oslo, Norway
[f] Department of Radiology, University of California San Diego, La Jolla, CA, USA
[g] Department of Neuroscience, University of California San Diego, La Jolla, CA, USA
[h] Department of Psychiatry, University of California San Diego, La Jolla, CA, USA

ARTICLE INFO

Article history:
Received 30 September 2013
Received in revised form 2 July 2014
Accepted 10 November 2014
Available online xxxx

Keywords:
Inflammation
Endothelial markers
Basal ganglia
Brain morphology

ABSTRACT

Background: Increased inflammation, endothelial dysfunction, and structural brain abnormalities have been reported in both schizophrenia and bipolar disorder, but the relationships between these factors are unknown. We aimed to identify associations between markers of inflammatory and endothelial activation and structural brain variation in psychotic disorders.

Methods: We measured von Willebrand factor (vWf) as a marker of endothelial cell activation and six inflammatory markers (tumor necrosis factor-receptor 1, osteoprotegerin, interleukin-1-receptor antagonist, interleukin-6, C-reactive protein, CD40 ligand) in plasma and 16 brain structures obtained from MRI scans of 356 individuals (schizophrenia spectrum; n = 121, affective spectrum; n = 95, healthy control subjects; n = 140). The relationship between the inflammatory and endothelial markers and brain measurements were investigated across groups.

Results: There was a positive association ($p = 2.5 \times 10^{-4}$) between plasma levels of vWf and total volume of the basal ganglia which remained significant after correction for multiple testing. Treatment with first generation antipsychotics was associated with basal ganglia volume only ($p = 0.009$). After adjusting for diagnosis and antipsychotic medication, vWf remained significantly associated with increased basal ganglia volume ($p = 0.008$), in particular the right globus pallidus ($p = 3.7 \times 10^{-4}$). The relationship between vWf and basal ganglia volume was linear in all groups, but the intercept was significantly higher in the schizophrenia group ($df = 2$, $F = 8.2$, $p = 3.4 \times 10^{-4}$).

Conclusion: Our results show a strong positive correlation between vWf levels and basal ganglia volume, in particular globus pallidus, independent of diagnosis. vWf levels were significantly higher in schizophrenia, which could indicate a link between endothelial cell activation and basal ganglia morphology in schizophrenia patients.

1. Introduction

A growing number of magnetic resonance imaging (MRI) studies have demonstrated structural brain abnormalities in schizophrenia and bipolar disorder, particularly reduced cortical volumes and thickness, enlarged ventricles and basal ganglia, and smaller hippocampal volumes (Arnone et al., 2009; Shepherd et al., 2012; Rimol et al., 2012; Rimol et al., 2010; Ellison-Wright and Bullmore, 2010; Ellison-Wright et al., 2008). However, the underlying biological mechanisms of the structural brain changes in patients with schizophrenia or bipolar disorder remain largely unknown.

A dysfunctional cross-talk between the immune system and the central nervous system (CNS) has long been proposed as a possible mechanism for schizophrenia and bipolar disorder (Potvin et al., 2008; Goldstein et al., 2009). Several lines of evidence have implicated tissue inflammation to be involved in the pathophysiology of both disorders (Dalman et al., 2008; Leonard, 2005; Brown and Derkits, 2010; Potvin et al., 2008; Goldstein et al., 2009; Berk et al., 2011), including elevated levels of C-reactive protein (CRP), interleukin (IL)-6 and sIL-2R, as a

* Corresponding author at: KG Jebsen Centre for Psychosis Research, Building 49, Division of Mental Health and Addiction, Oslo University Hospital Ullevål, Kirkeveien 166, N-0407 Oslo, Norway.
E-mail address: ingrid.dieset@medisin.uio.no (I. Dieset).

http://dx.doi.org/10.1016/j.schres.2014.11.006
0920-9964/

marker of T cell activation, and soluble tumor necrosis factor receptor type 1 (sTNF-R1), von Willebrand factor (vWf) as a marker of endothelial related inflammation and osteoprotegerin (OPG) as markers of inflammation (Potvin et al., 2008; Goldstein et al., 2009; Hope et al., 2010; Hope et al., 2009). In addition, Genome-wide association studies (GWAS) have identified genes involved in immune related activity as schizophrenia risk genes (Stefansson et al., 2009; Ripke et al., 2011), further supporting immune related disease mechanisms.

An important aspect of immune related mechanisms is related to endothelial cell activation. We have previously demonstrated increased plasma levels of vWf, as a marker of endothelial cell activation, to be associated with schizophrenia and bipolar disorder (Hope et al., 2009). Furthermore, we recently reported increased blood *NOTCH4* expression in bipolar disorder indicating involvement of endothelial related inflammation in the pathophysiology (Dieset et al., 2012a). As the brain is protected by the vascular endothelium at the blood brain barrier (BBB) (Wraith and Nicholson, 2012), studies investigating peripheral biological mechanisms in schizophrenia and bipolar disorders may not necessarily provide plausible explanations for the brain alterations. Lately, however, studies have indicated that the CNS is not as immune privileged as previously thought (Wraith and Nicholson, 2012), and circulating cytokines probably penetrate the BBB to some extent (Banks et al., 1995). Quite interestingly inflammatory activity might in fact be directly involved in BBB disruption (Capuron and Miller, 2011). In accordance with this, we reported a relationship between immune abnormalities and brain morphological alterations indicating a schizophrenia specific association between certain risk variants within the MHC complex and abnormalities of the ventricular system (Agartz et al., 2011). This is in line with a recent microarray study which reported increased inflammatory mRNA expression in schizophrenia brains (Fillman et al., 2013). It remains to be seen if inflammatory markers are related to brain morphology variation in psychotic disorders. Antipsychotic medication may also affect brain morphology (Chakos et al., 1998; Ho et al., 2011) and possibly mediate inflammatory activity (Dieset et al., 2012b), which makes it a potential important confounder.

The purpose of the present study was to explore a putative relationship between plasma levels of inflammatory and endothelial cell activation markers and brain structure measures obtained with MRI in a sample of schizophrenia and bipolar spectrum patients. The rationale for selection of the inflammatory markers was to represent distinct inflammatory pathways and endothelial activation. We hypothesized that a state of low-grade inflammation and endothelial activation would be associated with brain morphological abnormalities. As there are few previous studies in this research area, we explored any association between six inflammatory and one endothelial plasma marker and 16 a priori chosen brain regions of interest including distinct measures of cortical area and thickness, as well as subcortical volumes. We then performed followup analysis of all significant associations in order to explore potential diagnostic differences and confounding factors, with a specific focus on antipsychotic medication.

2. Methods

2.1. Study design and ethics

The study was conducted as part of the Thematically Organized Psychosis (TOP) Study at Oslo University Hospital and the University of Oslo, Norway. The present sample consisted of patients and controls, all included within a particular time period (August 2003–December 2008). The TOP Study was approved by the Regional Committee for Medical Research Ethics and the Norwegian Data Inspectorate and the biobank was approved by the Norwegian Directorate of Health.

The main criteria of inclusion in the TOP Study sample are SCID-I verified DSM-IV diagnoses of psychosis within schizophrenia spectrum or affective spectrum disorders. All subjects were between 18 and 65 years and had the ability to give written informed consent and to fully comprehend the presented information about the study. Criteria of exclusion were head injury, neurological disorder, mental retardation, autoimmune and infectious disorders and malignancies. All patients underwent a standardized protocol, including psychiatric interviews such as the Positive and Negative Syndrome Scale (PANSS), Inventory of Depressive Symptoms (IDS) and Young Mania Rating Scale (YMRS). The type and amount of illicit substances and number of international units of alcohol consumed over the past two weeks before examination were recorded. In addition, all participants were screened for and diagnosed for illicit substances and alcohol using the E module in the SCID-1 manual. Medication was recorded and confirmed by information from patient records and serum measurements.

Cumulative defined daily dosage (DDD) of antipsychotics (FGA and SGA), antidepressants, mood stabilizers and lithium were calculated according to the guidelines from the World Health Organization Collaborating Center for Drug Statistics Methodology (hhttp://www.whocc.no/atcdd).

A total of 216 patients and 140 healthy control subjects with eligible plasma samples and MRI brain scans were included in the study. The patients were divided into two groups of either schizophrenia spectrum or affective spectrum disorder. In the group with schizophrenia spectrum diagnosis were patients diagnosed with schizophrenia ($n = 69$), schizophreniform ($n = 8$), schizoaffective disorder ($n = 14$) or psychosis not otherwise specified ($n = 30$). In the affective spectrum group were patients diagnosed with bipolar disorder I ($n = 43$), bipolar disorder II ($n = 32$), bipolar disorder not otherwise specified ($n = 6$) or depressive psychosis ($n = 14$). The age and gender matched healthy control subjects ($n = 140$) were randomly drawn from a population registry and contacted by letter inviting them to participate in the study.

2.2. Measurements of inflammatory and endothelial markers

We used the seven markers that we previously investigated for role of inflammation and endothelial activation in psychosis (Hope et al., 2010; Hope et al., 2009; Dieset et al., 2012b). The rationale for selection of the inflammatory markers was to represent distinct inflammatory pathways. IL-6, sTNF-R1 and IL-1Ra are more specifically markers of activity in the upstream inflammatory pathways, whereas hsCRP is a downstream marker of inflammation. vWf is a marker of endothelial activity and CD40L of platelet mediated inflammation, whereas OPG is a soluble member of the tumor necrosis family. Increased levels of IL-6, CRP, OPG, CD 40L and TNF-α are associated with cerebral atrophy (Jefferson et al., 2007) in an elderly population. Increased levels of CRP, IL-6, TNF-α and vWf are associated with reduced executive functioning (Heringa et al., 2014). Finally, elevated levels of IL-1RA (Lotrich et al., 2014) are associated with poorer cognitive function in bipolar disorder and elevated levels of CRP with poorer cognitive function in bipolar disorder (Dickerson et al., 2013) and schizophrenia subjects (Dickerson et al., 2007).

Plasma levels of sTNF-R1, OPG, IL-1 receptor antagonist (IL-1Ra) and IL-6 were measured using enzyme immunoassays (EIA) obtained from R&D systems (Minneapolis, MN). Plasma sCD40 ligand (sCD40L) was analyzed using EIA obtained from Bender Medsystem (Vienna Austria), whereas high sensitivity CRP (hsCRP) and vWf were measured with EIA using antibodies from DakoCytomation (Oslo, Norway). vWf levels are given as plasma concentration percent (%), where the standard curve is based on samples from healthy individuals and normal range is set to 70–130%. Intra-and interassay coefficients of variance were <10% for all assays.

2.3. MRI acquisition

All participants underwent MRI scanning on a 1.5 T Siemens Magnetom Sonata scanner (Siemens Medical Solutions, Erlangen, Germany) equipped with a standard head coil. After a conventional

Please cite this article as: Dieset, I., et al., Association between altered brain morphology and elevated peripheral endothelial markers — Implications for psychotic disorders, Schizophr. Res. (2014), http://dx.doi.org/10.1016/j.schres.2014.11.006