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Increased peripheral levels of TARC/CCL17 in first episode psychosis patients

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ABSTRACT

Background: Evidence for a link between the pathophysiology of schizophrenia and the immune system is mounting. Altered levels of chemokines in plasma have previously been reported in patients with schizophrenia under antipsychotic medication. Here we aimed to study both peripheral and central chemokine levels in drug-naïve or short-time medicated first episode psychosis (FEP) patients.
Method: We analyzed nine chemokines in plasma and CSF from 41 FEP patients and 22 healthy controls using electrochemiluminescence assay.
Results: In plasma four chemokines; TARC/CCL17, eotaxin/CCL11, MDC/CCL22, IP-10/CXCL10 and in CSF one chemokine; IP-10/CXCL10 showed reliable detection in >50% of the cases. FEP patients displayed increased levels of TARC/CCL17 in plasma compared to healthy controls, 89.6 (IQR 66.2–125.8) pg/mL compared to 48.6 (IQR 28.0–71.7) pg/mL ($p = 0.001$). The difference was not attributed to confounding factors. Plasma TARC/CCL17 was not associated with PANSS, CGI or GAF scores, neither with cognitive functions. The chemokines eotaxin/CCL11, MDC/CCL22, IP-10/CXCL10 in plasma and IP-10/CXCL10 in CSF did not differ between FEP patients and controls.
Conclusion: In line with a previous study showing that chronic patients with schizophrenia display increased plasma TARC/CCL17 levels, we here found an elevation in FEP patients suggesting a role of TARC/CCL17 in early stages of schizophrenia. The exact mechanism of this involvement is still unknown and future longitudinal studies as well as studies of central and peripheral chemokine levels would be of great interest.

1. Introduction

Schizophrenia is a chronic disease affecting approximately 0.5% of the population worldwide (Simeone et al., 2015). The disease is characterized by positive symptoms, such as delusions and hallucinations, and negative symptoms, such as emotional flattening and social withdrawal (American Psychiatric Association, 2013). The patients also have cognitive dysfunctions and in drug-naïve first episode psychosis (FEP) patients, the greatest impairments have been found in verbal memory, speed of processing and working memory (Fatouros-Bergman et al., 2014).

A link between the immune system and the pathophysiology of schizophrenia has been suggested for long (Khandaker et al., 2015; Raymond and Williams, 1948). Although early childhood infections have been associated with an increased risk of schizophrenia (Dalman et al., 2008; Liang and Chikritzhs, 2012), substantial evidence of a central nervous system (CNS) immune activation was not provided until relatively lately where patients with schizophrenia were shown to have elevated levels of cytokines, i.e. interleukin (IL)-1β and IL-6 in the cerebrospinal fluid (CSF) (Sasayama et al., 2013; Schwieler et al., 2015; Söderlund et al., 2009; Wang and Miller, 2018). Meta-analysis of genome-wide association studies in schizophrenia has provided further evidence in this regard (Schizophrenia Working Group of the Psychiatric Genomics, 2014).

Cytokines and chemokines are signaling molecules of the immune system. Cytokines are key regulators of acute and chronic inflammation and help coordinate the function of both the innate and adaptive components of the immune system (Goldsmith et al., 2016). Chemokines

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are chemotactic cytokines that regulate trafficking of immune cells throughout the body (Ramesh et al., 2013). Previous studies have demonstrated that neurons and glial cells secrete chemokines and express their respective receptors (Asensio and Campbell, 1999; Bajetto et al., 2001; Mennicken et al., 1999). In the CNS, chemokines and their receptors are suggested to mediate immunoinflammatory responses, to regulate leukocyte infiltration through the blood-brain barrier during inflammatory or infectious diseases (Ragozzino, 2002; Reaux-Le Goazigo et al., 2013), to be involved in maintenance of homeostasis and to act as neurotransmitters and neuromodulators by regulating neurodevelopment and synaptic transmission (Gualtierotti et al., 2017; Hong et al., 2017; Reaux-Le Goazigo et al., 2013; Rostène et al., 2011).

The chemokines Thymus and activation-regulated chemokine (TARC/CCL17) and Macrophage-derived chemokine (MDC/CCL22 bind to and signal through the C-C chemokine receptor type 4 (CCR4) and are chemoattractants for CCR4-expressing Th2 lymphocytes, monocytes, monocyte-derived dendritic cells and natural killer cells (Richter et al., 2014; Saeki and Tamaki, 2006). TARC/CCL17 is a chemokine expressed in the thymus and associated with atopic dermatitis, atherosclerosis and cardiovascular disease (Weber et al., 2011; Ye et al., 2015). The chemokine has previously been found elevated in plasma of patients with schizophrenia with antipsychotic mediation (Hong et al., 2017). MDC/CCL22 is increased in plasma, both in FEP (Mantyla et al., 2015) and chronic patients, (Dimitrov et al., 2013; Mantyla et al., 2015; Ramsey et al., 2013). In chronic schizophrenia patients, some studies have shown low plasma levels of interferon-gamma-inducible protein-10 (IP-10/CXCL10) (Asevedo et al., 2013; de Campos-Carli et al., 2017; Dimitrov et al., 2013; Noto et al., 2015; Ramsey et al., 2013), a chemokine that attracts activated T cells, monocytes, and natural killer cells (Fallahi et al., 2017), whereas others did not detect any differences in plasma of chronic (Hong et al., 2017) or FEP patients (Mantyla et al., 2015). Although eotaxin/CCL11 (CCL11), a chemokine that recruits eosinophils (Wu et al., 2014) has been found elevated in plasma of chronic patients (Asevedo et al., 2013; Boll et al., 2017; Czepielewski et al., 2017; Hong et al., 2017; Noto et al., 2015; Pedrini et al., 2014; Ramsey et al., 2013; Teixeira et al., 2008), no alterations have been reported in plasma from recent onset schizophrenia patients (Pedrini et al., 2014) or FEP patients (Mantyla et al., 2015). To our knowledge, studies regarding CSF concentrations of these chemokines in schizophrenia are lacking.

The aim of the present study is to investigate if CSF and plasma chemokine concentrations are altered in FEP patients. We hypothesize that TARC/CCL17 and MDC/CCL22, but not IP-10/CXCL10 and eotaxin/CCL11 levels are elevated in FEP patients. If any alterations are found, we also aim to correlate levels of chemokines to psychotic symptoms and levels of functioning as well as to cognitive testings of verbal memory, speed of processing and working memory.

2. Methods

2.1. Subject population

This study was part of Karolinska Schizophrenia Project (KaSP), a multidisciplinary research consortium that investigates the pathophysiology of schizophrenia. The study was conducted according to the Declaration of Helsinki principles and was approved by the Stockholm Regional Ethics Committee (2010/879-31-1). All participants were included between January 2011 and February 2014 and signed consent forms were obtained from all individuals.

2.2. First episode psychosis patients

Forty-two consecutive FEP patients, aged 18–42 years, seeking health care for psychotic symptoms for the first time, were recruited from psychiatric emergency wards and in- and outpatient facilities from three psychiatric clinics in Stockholm. Exclusion criteria were treatment with antipsychotics for >30 days, severe somatic and neurological disease, current substance abuse (except nicotine use) and autism-spectrum disorder. These criteria were ruled out through clinical examination, medical history, routine laboratory tests including screening for drugs and brain magnetic resonance imaging (MRI). One patient was excluded because of a brain tumor found on MRI, resulting in a total number of 41 patients; 26 males and 15 females. The patients' medication was decided by the treating clinician.

Diagnosis according to DSM-IV was established based on a structured clinical interview (SCID-I) at the time of inclusion, or a consensus diagnostic procedure based on medical records supervised by an experienced psychiatrist (LF). Patients met the diagnostic criteria for schizophrenia ($n = 12$), schizophreniform disorder ($n = 15$), schizoaffective syndrome ($n = 1$), brief psychotic disorder ($n = 1$), delusional disorder ($n = 3$), psychosis not otherwise specified ($n = 8$) and severe depression with psychotic features ($n = 1$). The patients' diagnoses were reassessed after 1.5 years, either with SCID-I or a consensus diagnostic procedure based on medical records, and met the criteria for the diagnoses of schizophrenia ($n = 26$), schizoaffective disorder ($n = 3$), brief psychotic disorder ($n = 1$), delusional disorder ($n = 4$), psychosis not otherwise specified ($n = 5$) and no psychotic diagnose ($n = 2$).

All patients underwent clinical characterization using the Positive and Negative Syndrome Scale (PANSS), the Global Assessment of Functioning (GAF), Clinical Global Impression (CGI), Alcohol Use Disorders Identification Tests (AUDIT) and Drug Use Disorders Identifications Tests (DUDIT). All raters for the PANSS attended training sessions and yearly repeated assessments showed a correlation coefficient between raters of 0.75 for PANSS scores. The Measurement and Treatment Research to Improve Cognition in Schizophrenia Consensus Cognitive Battery (Nuechterlein et al., 2008) was used to evaluate cognitive function and one psychologist (HFB) managed all tests. Following tests were used for each cognitive domain: Verbal learning (Hopkins Verbal Learning Test-Revised); Speed of processing (Brief Assessment of Cognition in Schizophrenia: Symbol Coding, Category Fluency: Animal Naming, Trail Making Test: Part A), Working memory (Wechsler Memory Scale-3rd Edition: Spatial Span, Letter-Number Span). Full details of the study design and patient characteristics have been published elsewhere (Orhan et al., 2017).

2.3. Healthy control subjects

Twenty-two controls (11 males and 11 females) living in Stockholm were recruited by advertisement. Exclusion criteria were neurologic disease, severe somatic disease, previous or current use of illegal drugs and first-degree relatives with psychotic or bipolar disorder. Eligibility was determined by clinical examination, medical history, routine laboratory tests and MRI examination, as evaluated by an experienced neuroradiologist at the MR Centre, Karolinska University Hospital, Solna. One individual exhibited signs of demyelinating disease on MRI and oligoclonal bands in CSF, but as the clinical neurological exam was normal and there was no history of relevant neurological symptoms, the subject did not fulfill criteria for multiple sclerosis or any other clinically isolated syndrome. Test results were similar to the other controls and therefore this subject was not excluded from the analysis. Smoking was permitted. Previous or current psychiatric illness was excluded by clinical examination and The Mini International Neuropsychiatric Interview (M.I.N.I.) performed by either a resident or a specialist in psychiatry. The subjects underwent the same cognitive testing procedure as the patients.

2.4. CSF sampling

Lumbar puncture for all participants was performed between 7.45 am–1.15 pm and the subjects were instructed to avoid physical activity during the preceding 8 h. A disposable atraumatic needle (22G

Sprotte, Geisingen, Germany) was inserted at the L4–5 level, with the subject in the right decubitus position. CSF was frozen at −80 °C within 1 h of sampling until analysis, following centrifugation (Sigma 5810R, Eppendorf, Hamburg, Germany) at 1438*g* for 10 min to separate cells and supernatant, respectively.

2.5. Plasma isolation

Peripheral blood was collected in 10 mL tubes containing EDTA (BD Vacutainer®; BD Hemograd, K2 EDTA) using standard venipuncture techniques at the same time as the CSF collection. Plasma was separated by centrifugation at 2900 rpm for 15 min within 1 h of collection and stored at −80 °C until analysis.

2.6. Analysis of chemokines

We analyzed MIP-1α/CCL3, MIP-1β/CCL4, eotaxin/CCL11, MCP-4/CCL13, TARC/CCL17, MDC/CCL22, eotaxin-3/CCL26, IL-8/CXCL8 and IP-10/CXCL10 in plasma and CSF using an electrochemiluminescence method (MesoScale, Gaithersburg, MD, USA; human chemokine panel 1 kit (cat no. N05047A-1)). The assays were performed following the instructions from the manufacturer (http://www.mesoscale.com). The sample volume was 25 μL and all samples were analyzed in duplicates. The intra-assay coefficient of variation (% CV) was below 25%. Detection limit was decided with respect to the level of the noise/signal ratio and the lower limit of detection was set to 2.5 SD above background when blank sample (analyze buffer) was analyzed, and were as follows in plasma; MIP-1α/CCL3 (9.58 pg/mL), MIP-1β/CCL4 (11.2 pg/mL), eotaxin/CCL11 (13.0 pg/mL), MCP-4/CCL13 (3.01 pg/mL), TARC/CCL17 (0.741 pg/mL), MDC/CCL22 (12.0 pg/mL), eotaxin-3/CCL26 (6.32 pg/mL), IL-8/CXCL8 (809 pg/mL) and IP-10/CXCL10 (0.915 pg/mL) and in CSF; MIP-1α/CCL3 (12.5 pg/mL), MIP-1β/CCL4 (8.84 pg/mL), eotaxin/CCL11 (8.5 pg/mL), MCP-4/CCL13 (16.8 pg/mL), TARC/CCL17 (0.70 pg/mL), MDC/CCL22 (22.4 pg/mL), eotaxin-3/CCL26 (5.51 pg/mL), IL-8/CXCL8 (333 pg/mL) and IP-10/CXCL10 (2.1 pg/mL).

2.7. Statistical analysis

The normality of data was determined using Shapiro-Wilk test. Demographic data and clinical scores are presented as median [Interquartile range (IQR)] and were compared between groups using Mann-Whitney *U* test (when data was not normally distributed) or Student's *t*-test (when data was normally distributed) for continuous variables and the chi-square for categorical variables. Chemokine levels are presented as median [Interquartile range] and were compared using the Mann-Whitney U test. Bonferroni correction was used in the comparison of chemokine levels between healthy controls and FEP patients, giving an α-threshold of 0.003 (0.05/18). The levels of chemokines in patients diagnosed with schizophrenia or schizoaffective disorder were compared with the other patients using Mann-Whitney U test. To assess potential confounders, we performed Spearman's correlations with the analyzed chemokines and also used binary logistic regression with FEP/control as the dependent variable and the analyzed chemokine, gender, nicotine use and antipsychotic medication as the independent. Associations between TARC/CCL17 levels and clinical ratings and cognitive measures were assessed using Spearman correlations due to non-normality in data. All reported p-levels are two-sided and statistical significance was considered when $p \leq 0.05$. All analyses were performed using Prism version 7.0 (GraphPad Software Inc.) or SPSS Statistics version 20.0 (IBM Inc.).

3. Results

3.1. Demographics

Clinical and demographic characteristics of the forty-one FEP patients (26 male and 15 female) and 22 healthy controls (11 male and 11 female) are presented in Table 1. Median age in FEP patients was 28.0 (IQR: 24.0–33.5) years and 25.0 (IQR: 21.75–28.25) years in healthy controls ($p = 0.079$). BMI did not differ between patients and controls ($p = 0.24$). Nicotine use was registered for 38 FEP patients and all ($n = 22$) healthy controls. Ten (26%) of the FEP patients and two (9%) of the healthy controls used nicotine and of those three (7.9%) of the FEP patients and none of the healthy controls were smoking and the others used snuff. Median duration of untreated psychosis (DUP) in patients was 5.0 (IQR: 2–18) months. Twenty-four (58.5%) of the FEP patients were drug-naïve to antipsychotic medication. One of the patients and none of the controls reported using anti-inflammatory medication (diclofenac) on regular basis.

3.2. Plasma chemokines in FEP patients and healthy controls

In plasma, eotaxin/CCL11 was detectable in 26 FEP patients and 11 healthy controls, IP-10/CXCL10 and MDC/CCL22 in 40 FEP patients and 21 healthy controls and TARC/CCL17 in 37 FEP patients and 19 healthy controls. The other chemokines analyzed (eotaxin-3/CCL26, IL-8/CXCL8, MCP-4/CCL13, MIP-1α/CCL3 and MIP-1β/CCL4) had <50% reliable detectable values and are therefore not reported.

We found no significant correlations between plasma chemokines and freezer storage time (TARC/CCL17: $n = 56$, $r = 0.098$, $p = 0.47$; eotaxin/CCL11: $n = 37$, $r = -0.092$, $p = 0.59$; MDC/CCL22: $n = 61$, $r = -0.11$, $p = 0.42$; IP-10/CXCL10: n = 61, $r = -0.20$, $p = 0.12$).

Plasma TARC/CCL17 concentration was significantly higher in FEP patients (n = 37; 89.62 [IQR 66.15–125.82]) pg/mL compared to healthy controls ($n = 19$; 48.60 [IQR 28.03–71.71]) pg/mL ($p = 0.001$, $p = 0.018$, following Bonferroni correction) (Fig. 1). Plasma eotaxin/CCL11, IP-10/CXCL10 and MDC/CCL22 levels did not differ significantly between FEP patients and healthy controls (Fig. 1). The patient medicated with diclofenac displayed similar levels of chemokines in plasma as the other patients (TARC/CCL17 31.87 pg/mL, eotaxin/CCL11 154.77 pg/mL, IP-10/CXCL10 173.59 pg/mL and MDC/CCL22 698.90 pg/mL) and was therefore not removed from the analysis. Plasma levels of chemokines did not associate with age, gender, BMI, nicotine use or antipsychotic medication. DUP was negatively associated with levels of IP-10/CXCL10 in plasma (spearman rho −0.347, $p = 0.038$), but not with the other chemokines. Patients treated with antipsychotics showed similar TARC/CCL17 concentrations as drug-naïve patients, ($n = 14$; 93.77 [IQR: 58.29–192.69]) vs ($n = 23$; 89.62 [IQR: 67.35–102.66]) and similar levels of the other chemokines as well (data not shown). When stratified by gender, levels of TARC/CCL17 were significantly higher in male FEP patients ($n = 24$; 93.79 [IQR: 78.15–128.07]) pg/mL compared to male healthy controls ($n = 10$; 47.41 [IQR: 27.72–74.11]) pg/mL ($p = 0.008$), and higher but not significant in female patients ($n = 13$; 75.67 [IQR: 41.00–123.31]) compared to female healthy controls ($n = 9$; 56.35 (IQR: [6.35–18.00]) pg/mL ($p = 0.117$), the latter possible due to lack of power. When adjusting for gender, nicotine use and antipsychotic medication, TARC was significantly different between FEP patients and healthy controls ($p = 0.015$). Levels of chemokines were similar between the group of patients diagnosed with schizophrenia and schizoaffective disorder at a 1.5 year follow-up examination and the group of patients diagnosed with brief psychotic disorder, delusional disorder, psychosis not otherwise specified and no psychotic diagnose (data not shown).

3.3. CSF chemokines in FEP patients and healthy controls

In CSF we detected IP-10/CXCL10 in 39 patients and 21 controls. The other chemokines analyzed (eotaxin/CCL11, eotaxin-3/CCL26, IL-8/CXCL8, MCP-4/CCL13, MDC/CCL22, MIP-1α,/CCL3 MIP-1β/CCL4 and TARC/CCL17) had <50% reliable detectable values and are therefore

Table 1
Demographics and clinical characteristics of FEP patients and healthy controls.

Characteristic	Median [Interquartile range] (n)		*P*-value
	Healthy controls ($n = 22$)	FEP patients ($n = 41$)	
Age, years	25.0 [21.8–28.4] (22)	28.0 [24.0–33.5] (41)	0.079[a]
Gender, male/female	11/11	26/15	0.303[b]
BMI, kg m^{-2}	22.4 [20.6–25.5] (21)	21.6 [20.3–23.9] (39)	0.827[c]
Nicotine, %,	9.1% (22)	21.3% (38)	0.108[b]
Smoking, %	0 (22)	7.9% (38)	–
DUP, months		5.0 [2.0–18] (39)	
Under antipsychotic treatment, %	0%	58.5% (41)	–
Under antidepressive treatment %	0%	12.2% (41)	–
Under anti-inflammatory treatment %	0%	2.4% (41)	
PANSS			
Positive	–	19.0 [14.5–23.5] (41)	–
Negative	–	13.0 [10.0–20.0] (41)	–
General	–	38.5 [29.5–45.5] (41)	–
Total	–	75.0 [60.0–85.0] (41)	–
Level of functioning			
GAF symptom	–	31.0 [21.0–37.5] (41)	–
GAF function	–	40.0 [33.5–51.0] (41)	–
CGI scores	–	4.5 [4.0–5.0] (41)	–

Abbreviations: BMI = Body Mass Index, DUP = duration of untreated psychosis, PANSS = Positive and Negative Syndrome Scale, GAF = Global Assessment of Functioning, CGI = Clinical Global Impression.
[a] Mann Whitney U test due to non-normality in data.
[b] Chi-square test.
[c] 2 tailed Student's *t*-test.

not reported. The CSF levels of IP-10/CXCL10 did not correlate with the freezer storage time ($n = 60$, $r = 0.024$, $p = 0.86$).

CSF levels of IP-10/CXCL10 did not differ between patients ($n = 39$) and controls ($n = 21$) (Fig. 1) nor between drug-naïve patients (n = 23) and patients medicated with antipsychotics ($n = 16$) (data not shown). The patient medicated with diclofenac displayed a concentration of IP-10/CXCL10 within the range of the other patients (245.42 pg/mL) and was therefore not removed from the analysis. CSF IP-10/CXCL10 did not associate with age, gender, BMI, DUP, nicotine use or antipsychotic medication. CSF and plasma levels of IP-10/CXCL10 did not correlate in neither FEP patients, healthy controls (spearman's rho 0.21, $p = 0.19$ respective −0.12, $p = 0.62$) nor in the groups combined (spearman's rho 0.10, $p = 0.44$). The group of patients with schizophrenia or schizoaffective disorder at a 1.5 year follow-up examination did not differ from the other patient in levels of IP-10/CXCL10 (data not shown).

3.4. Associations between TARC/CCL17 levels and clinical rating scores and cognitive measures in first episode psychosis patients

Plasma concentrations of TARC/CCL17 were not associated with PANSS positive ($p = 0.69$), PANSS negative ($p = 0.37$), PANSS general ($p = 0.59$), PANSS total ($p = 0.56$), GAF symptoms ($p = 0.35$), GAF function ($p = 0.08$) nor CGI ($p = 0.13$). Moreover, no associations that held for Bonferroni corrections were found between TARC/CCL17 levels and verbal memory ($p = 0.65$), speed of processing ($p = 0.41$, $p = 0.12$, $p = 0.48$) or with working memory ($p = 0.83$, $p = 0.04$) measured with MATRICS.

4. Discussion

The main finding of the present study is that the chemokine TARC/CCL17 was elevated in the plasma of FEP patients compared to healthy controls, which did not seem to be attributed to confounding factors. This elevation indicates a role of TARC/CCL17 in early stage of the disease and is in line with a previous study showing increased plasma levels in chronic patients (Hong et al., 2017). We did not find any association between plasma TARC/CCL17 levels and symptom ratings or cognitive performance and it is presently unclear whether the increased concentration of TARC/CCL17 is part of the pathogenesis of schizophrenia, or reflect a compensatory mechanism serving to counteract for other pathophysiological events of the disease, e.g. activation of brain IL-1β and IL-6 (Sasayama et al., 2013; Söderlund et al., 2009). Reports of TARC/CCL17 concentrations in other psychiatric disorders are scarce. One study showed lower CSF TARC/CCL17 levels in suicide attempters compared to healthy controls (Janelidze et al., 2013). At a follow-up occasion 12 years after the initial suicide attempt, the suicide attempters displayed decreased plasma levels of TARC/CCL17 compared to psychiatric patients that had not tried to commit suicide (Janelidze et al., 2013). Furthermore, male patients with post-traumatic stress disorder showed significantly lower plasma TARC/CCL17 levels compared to controls whereas in female patients a trend towards higher plasma TARC/CCL17 levels compared to controls was observed (Dalgard et al., 2017). In children with autism, increased plasma TARC/CCL17 levels have been reported (Al-Ayadhi and Mostafa, 2013). '.

Patients with schizophrenia generally show a life-span that is 12–15 years shorter than the general population. Ischemic heart disease is the most common cause of death in patients with schizophrenia (Crump et al., 2013; Olfson et al., 2015). Interestingly, TARC/CCL17 has been linked to cardiovascular disease. In humans, TARC/CCL17 associated to type and severity of coronary heart disease and the authors suggested that TARC/CCL17 could be used as a surrogate marker for cardiovascular screening or a predictor of future cardiovascular events. (Ye et al., 2015). Further, in mice, TARC/CCL17-expressing dendritic cells are accumulated in atherosclerotic lesions and TARC/CCL17 deficiency causes a reduction of atherosclerosis in atherosclerosis-prone mice and administration of an antibody blocking TARC/CCL17 reduces atheroprogression (Weber et al., 2011; Ye et al., 2015). One may thus speculate that TARC/CCL17 plays a pathophysiological role, constituting a link between schizophrenia and its cardiovascular comorbidity. Based on the present findings, the relationship between TARC/CCL17 and early signs of atherosclerosis will be important to study in psychosis patients.

In the present study, no differences in plasma eotaxin/CCL11 levels were found between FEP patients and healthy controls. This is in agreement with previous studies of plasma eotaxin/CCL11 levels in recent onset schizophrenia (Pedrini et al., 2014) and FEP patients (Mantyla et al., 2015). However, several studies report increased plasma eotaxin/CCL11 levels in chronic, medicated schizophrenia patients

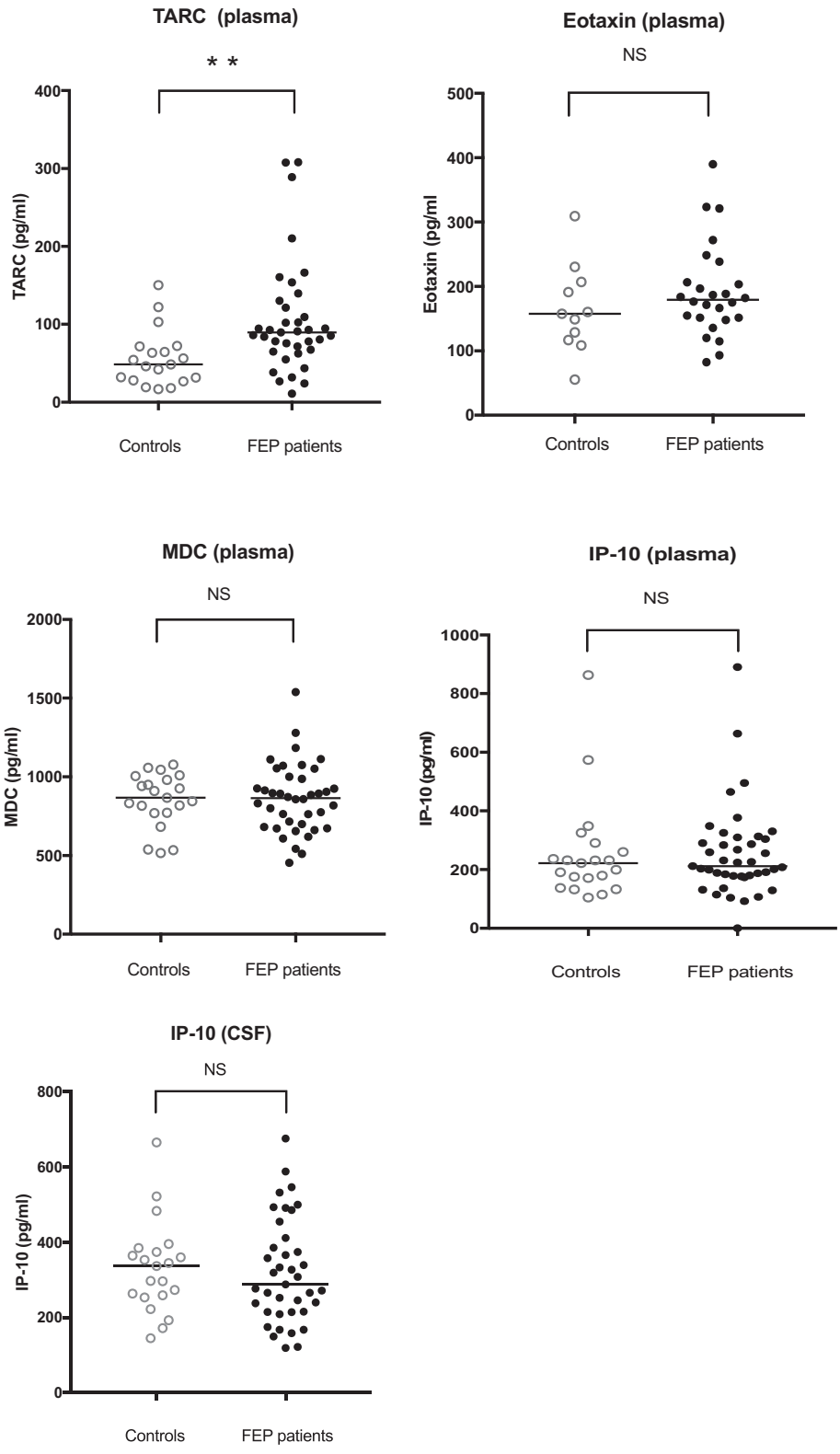

Fig. 1. Chemokines levels in FEP patients and healthy controls.

(Asevedo et al., 2013; Boll et al., 2017; Czepielewski et al., 2017; Hong et al., 2017; Noto et al., 2015; Pedrini et al., 2014; Ramsey et al., 2013; Teixeira et al., 2008). Cannabis smoking (but not tobacco) has been associated with higher levels of eotaxin/CCL11 in plasma (Fernandez-Egea et al., 2013). This was not adjusted for in previous studies, while in our study patients with drug-abuse were excluded, which also could explain the discrepant results.

Our findings of no significant differences in plasma IP-10/CXCL10 between patients and controls are in agreement with a previous study of FEP patients (Mantyla et al., 2015) and a study of chronic, medicated

patients (Hong et al., 2017). Studies of CSF chemokines in schizophrenia are to our knowledge still lacking. In the present study, the only chemokine detectable in CSF, IP-10/CXCL10, did not differ between patients and controls. This may suggest a role of IP-10/CXCL10 in later stages of the disorder and/or effects of long-term medication.

In contrast to previous studies showing elevated plasma levels of MDC/CCL22 both in FEP (Mantyla et al., 2015) and chronic patients, (Dimitrov et al., 2013; Mantyla et al., 2015; Ramsey et al., 2013), we did not observe any differences in plasma MDC/CCL22 levels. This discrepancy could be explained by several confounding factors; in the previous study of FEP patients, the patients had received medication for a longer time, more patients were smokers compared to the patients included in the present study and since DUP was not reported in the other studies, differences regarding this parameter could not be ruled out.

The strength of the present study is that it includes plasma and CSF from well-characterized FEP patients either naïve to antipsychotic medication or under short time treatment, and without substance abuse.

Limitations are the small sample size. The decision to exlude patients with drug-abuse makes the results less generalizable since cannabis-use is reported in 33.7% of patients with first episode psychosis (Myles et al., 2016). Nevertheless this is beneficial when the aim is to study the underlying pathyphyshiological mechanisms of the disease itself, since associations of cannabis and chemokine leves have previously been suggested (de Campos-Carli et al., 2017).

Altogether our findings of elevated TARC/CCL17 in FEP patients indicate a role of TARC/CCL17 in early stage of schizophrenia. Future longitudinal studies investigating the association of TARC/CCL17 and monoaminergic neurotransmission as well as other putative disease markers would be of great interest.

Collaborators

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Contributors

Sophie Erhardt and Göran Engberg designed the study. Anna Malmqvist and Sophie Erhardt drafted the report. Anna Malmqvist, Lilly Schwieler and Funda Orhan were responsible for the statistical analyses. Anna Malmqvist, Helena Fatouros-Bergman, Fredrik Piehl and Lena Flyckt collected all clinical data. Funda Orhan and Lilly Schwieler performed the cytokine analysis. All authors contributed to the interpretation of the results, provided critical revision of the report and approved the final manuscript.

Conflicts of interest

SC has received grant support from AstraZeneca as a co-investigator, and has served as a one-off speaker for Otsuka-Lundbeck. SC's spouse is an employee of Swedish Orphan Biovitrum. SE has received grant support from AstraZeneca and Jansen Pharmaceuticals as principal investigator and has been a speaker for Roche Pharmaceuticals, Astra Zeneca, Eli Lilly and Bristol Myers Squibb.

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