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TNF- α and IL-6 are Associated with the Deficit Syndrome and Negative Symptoms in Patients with Chronic Schizophrenia

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Abstract

Introduction—Increased inflammatory markers have been found in patients with chronic schizophrenia, and have been associated with negative symptoms. The deficit syndrome is a distinct subtype of schizophrenia, characterized by primary and enduring negative symptoms.

Method—We measured inflammatory markers in patients with and without deficit schizophrenia and controls.

Results—Using multivariate analyses, tumor necrosis factor (TNF)- α and interleukin-6 were associated with the deficit syndrome, and TNF- α predicted blunted affect, alogia, and total negative symptoms.

Conclusions—Findings suggest that deficit schizophrenia subtype is associated with increased inflammation and immunotherapies may be a novel target for negative symptoms.

Keywords

Schizophrenia; Deficit Syndrome; Negative Symptoms; Cytokines; Inflammation

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conflicts of interest

The authors report no conflicts of interest related to this study.

Contributors

David Goldsmith, MD managed the literature searches, statistical analyses, and wrote the first draft of the manuscript. All authors contributed to and have approved the final manuscript.

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1. Introduction

Inflammation has been posited as a potential mechanism underlying the development and progression of schizophrenia (Consortium, 2014; Miller and Goldsmith, 2017; Sekar et al., 2016). Meta-analyses have demonstrated that patients with schizophrenia reliably exhibit increased markers of inflammation (Goldsmith et al., 2016; Miller et al., 2011; Potvin et al., 2008). Furthermore, there is a growing literature showing that increased inflammatory cytokines may be linked to negative symptoms in patients with schizophrenia (Asevedo et al., 2014; El Kissi et al., 2015; Garcia-Rizo et al., 2012; Liu et al., 2012; Noto et al., 2015; Stojanovic et al., 2014; Xiu et al., 2014).

The deficit syndrome (Carpenter et al., 1988; Kirkpatrick et al., 2001) is a subgroup of patients with schizophrenia who have primary (i.e., idiopathic) and enduring negative symptoms that are not secondary to other aspects of the disorder, such as psychosis, depression, medication effects, etc. Previous work has demonstrated that patients with deficit schizophrenia may also have a distinct neurobiology within the larger class of patients with schizophrenia (Benoit et al., 2012; Fischer et al., 2012; Kanahara et al., 2013; Mucci et al., 2007; Voineskos et al., 2013). One aspect of this distinct neurobiology may involve the immune system. To our knowledge, only one study (Garcia-Rizo et al., 2012) has compared inflammatory markers in patients with and without deficit schizophrenia. This study found higher concentrations of C-reactive protein (CRP) and interleukin (IL)-6 in newly-diagnosed, antipsychotic naïve subjects with deficit schizophrenia. Nevertheless, whether a broader array of inflammatory markers are related to deficit schizophrenia and whether antipsychotic treatment may contribute to this relationship in patients more characteristic of the syndrome (i.e., individuals with chronic illness on medication) remains unknown. To address these questions, we measured a larger panel of inflammatory markers in a group of chronic patients with schizophrenia treated with antipsychotics. Inflammatory markers included those found to be elevated in individuals with chronic schizophrenia on antipsychotic medications in a recent meta-analysis (Goldsmith et al., 2016): interferon (IFN)- γ , IL-1 β , IL-6, soluble IL-2 receptor (sIL-2R), and tumor necrosis factor (TNF)- α . We hypothesized that there would be significant differences in inflammatory marker concentrations between patients with schizophrenia with and without deficit schizophrenia and that inflammatory markers would be associated with symptoms that characterize the deficit syndrome as well as other negative symptoms.

2. Experimental/Materials and methods

All procedures were approved by the Institutional Review Board of Augusta University. Fifty-six patients with SCID diagnoses of DSM-IV schizophrenia, schizoaffective disorder, and psychosis NOS, and 28 healthy controls who provided written informed consent were included in the study. Deficit schizophrenia classification was determined using the Proxy for the Deficit Syndrome employing the Positive and Negative Symptom Scale (Goetz et al., 2007; Kirkpatrick et al., 1993). Patients were screened for a history of any immune disorders, HIV, hepatitis B and C, current infection including urinary tract infection, and illicit drug use in the past 30 days. Exclusion criteria also included use of any anti-inflammatory drugs, including non-steroidal anti-inflammatories (NSAIDs), corticosteroids

or other immunomodulatory agents. They could not have taken an antibiotic within the past two weeks (based on self-report and review of the electronic medical record). Additionally, patients were also screened with a fasting complete blood count, comprehensive metabolic panel, lipid panel, urinalysis and urine drug screen.

Fasting blood samples were collected in EDTA tubes and centrifuged at 4000 rpm for 10 minutes at room temperature. Plasma was extracted and stored at -70°C until assay; samples were run in three different batches. Concentrations of IFN- γ , IL-1 β , IL-6, sIL-2R, and TNF- α . were measured by multiplexing with a Luminex 200 System with Human Cytokine/Chemokine multi-plex Antibody Bead Panel (Invitrogen). Mean intra-assay coefficients of variation (CV) ranged from 12–21%, and inter-assay CVs from 6–11%. Three samples for IL-6, TNF- α , and sIL-2R were below the limits of assay detection (all from healthy controls), and 11 and 14 samples were below assay detection for IL-1 β and IFN- γ , respectively (IL-1 β : 5 from non-deficit patients; 6 from healthy controls; IFN- γ : 5 from non-deficit patients; 9 from healthy controls). All results are expressed as pg/ml.

Differences in demographic and clinical variables among groups were determined using one-way analysis of variance (ANOVA) for continuous variables and chi-square for categorical variables. To examine associations between inflammatory markers and group assignment, multivariate general linear models (GLM) were performed with the inflammatory markers as dependent variables and diagnostic group as a fixed factor. Relevant covariates (demographic and/or clinical variables that differed among groups) were also included in the models. After establishing the overall significance of the model (Roy's Largest Root), the relative significance of each inflammatory marker was examined. In the initial GLM, patients versus controls was the fixed factor. In subsequent models, group assignment was defined as either deficit versus non-deficit patients versus controls or deficit versus non-deficit patients alone. Stepwise, backward linear regression models were used to determine the relationship between relevant inflammatory markers and symptoms that characterize deficit schizophrenia (blunted affect and alogia), as well as total PANSS negative and positive symptom subscale scores. Because the inflammatory markers were not normally distributed, all statistical analyses were conducted using natural log-transformed values.

3. Results

Sociodemographic, clinical characteristics and concentrations of inflammatory markers for the sample are shown in Table 1. Significant differences were found between patients and controls for the number of cigarettes smoked daily [$F(1,82)=12.15$, $p=0.001$], body mass index (BMI) [$F(1,82)=3.17$, $p=0.079$], education [$\chi^2(1)=10.55$, $p=0.001$], and race [$\chi^2(2)=5.51$, $p=0.064$]. These variables were included as covariates in the multivariate GLM. The overall model for the association between inflammatory markers and group assignment of patients versus controls was not significant [$F(5,52)=0.472$, $p=0.796$], and none of the inflammatory markers were significantly associated with group status.

Examination of patients with deficit ($n=17$) versus non-deficit schizophrenia ($n=29$) versus controls ($n=17$) revealed significant differences among the groups on number of cigarettes smoked daily [$F(2,81)=6.09$, $p=0.003$], race [$\chi^2(4)=10.95$, $p=0.027$], and education

$[\chi^2(2)=10.91, p=0.004]$, all of which were included as covariates in the GLM. A significant group by inflammatory marker profile interaction was seen for the whole group $[F(5,54)=2.44, p=0.046]$, with TNF- α $[F(2,57)=3.51, p=0.036]$ and IL-6 $[F(2,57)=3.89, p=0.026]$ accounting for the group differences. As shown in Figure 1a, TNF- α was significantly higher in patients with deficit schizophrenia compared to both healthy controls and patients without deficit schizophrenia using Least Square Difference (LSD) post hoc analyses (deficit vs control, $p<0.005$; deficit vs non-deficit, $p<0.01$). IL-6 was also significantly higher in patients with deficit schizophrenia compared to both healthy controls and non-deficit patients in LSD post hoc analyses (deficit vs control, $p=0.044$; deficit vs nondeficit, $p=0.036$). Though BMI was not significantly different between groups, given known associations between BMI and inflammatory markers (Schmidt et al., 2015; Steiner et al., 2014) we tested the potential influence of BMI in univariate general linear models with both TNF and IL-6. The same predictors as noted above were also included in the model. BMI was not significant in either model, and both TNF $[F(1,74) = 3.50, p = 0.035]$ and IL-6 $[F(1,74) = 3.22, p = 0.046]$ remained significantly associated with group assignment.

The two patient groups (deficit versus non-deficit) significantly differed in current antipsychotic dose (chlorpromazine [CPZ] equivalents) $[F(1,54) = 2.97, p = 0.09]$ and race $[\chi^2(2)=7.24, p=0.027]$. GLM models comparing the two patient groups, including CPZ equivalents and race as covariates, revealed an overall group effect $[F(5,38)=2.48, p=0.049]$, with TNF $[F(1,42)=6.41, p=0.015]$, and IL-6 $[F(1,42)=6.57, p=0.0214]$ showing a significant association with group status. As indicated above, to test the influence of BMI, we conducted univariate general linear models with both TNF and IL-6 with BMI in the model. BMI was not significant in either model, and both TNF $[F(1,51) = 6.94, p = 0.011]$ and IL-6 $[F(1,51) = 6.03, p = 0.017]$ remained significantly associated with patient group assignment.

In linear regression models, increases in plasma TNF- α were significantly associated with increased blunted affect ($\beta=0.31, p=0.018$) and alogia ($\beta=0.30, p=0.024$), as well as increased total PANSS Negative scores ($\beta=0.31, p=0.012$), after controlling for CPZ equivalents and race (Figure 1b). No associations were seen between TNF- α and PANSS Positive or General scores. No associations were found with IL-6 concentrations and PANSS negative symptoms. Linear regression models were also rerun with BMI in the model. BMI was not associated with negative symptoms, and the significant associations between TNF and negative symptoms were unchanged.

4. Discussion

TNF- α and IL-6 were elevated in patients with deficit schizophrenia compared to non-deficit patients and healthy controls, indicating that a broader array of inflammatory markers might be related to the deficit subtype in patients with chronic schizophrenia prescribed antipsychotics. TNF- α was also found to be associated with deficit schizophrenia in multivariate models, while controlling for significant clinical variables, including antipsychotic dose. These findings support the notion that deficit schizophrenia may represent a distinct pathophysiology involving the immune system independent of antipsychotic medication and other relevant variables including race, education, and

smoking status. Finally, TNF- α was associated with the severity of PANSS negative symptoms, specifically with items on the PANSS that are included in deficit schizophrenia categorization (Kirkpatrick et al., 1993). One limitation of these analyses is that a number of subjects had inflammatory markers below the limits of detection, which decreased our power to find differences among groups. Nevertheless, moderate to large effect sizes were found for TNF and IL-6 (Cohen's d of 0.61 for TNF and 0.59 for IL-6) and power was 0.67 and 0.64, respectively.

These findings are consistent with previous work demonstrating elevated TNF- α and IL-6 in patients with chronic schizophrenia (Goldsmith et al., 2016) and elevated IL-6 and CRP were elevated in newly-diagnosed, antipsychotic-naïve patients with deficit schizophrenia (Garcia-Rizo et al., 2012). Moreover, these data further support the association of inflammatory markers with negative symptoms. Negative symptoms do not typically respond to conventional antipsychotic treatment (Davis et al., 2014), and negative symptoms in patients with deficit schizophrenia may be particularly treatment resistant (Kopelowicz et al., 2000; Lindenmayer et al., 2007).

The association of increased inflammation and negative symptoms of the disorder suggests that inflammation may represent a novel treatment target in deficit schizophrenia. TNF- α may be a critical target because it is one of the most consistently identified inflammatory markers found to be elevated in patients with schizophrenia and is associated with negative symptoms. In addition, administration of the TNF- α antagonist infliximab to patients with treatment-resistant major depressive disorder and increased inflammation led to decreases in symptoms of anhedonia and psychomotor slowing (Raison et al., 2013), which may overlap with transdiagnostic concepts of positive and negative valence systems (Insel et al., 2010). Indeed, data demonstrate that inflammatory cytokines can target cortico-striatal circuits involved in motivation and motor activity (Capuron et al., 2012; Felger et al., 2016), and decreased activation of the ventral striatum to reward has been found in patients with schizophrenia in association with negative symptoms (Juckel et al., 2006). Moreover, patients with deficit schizophrenia have been shown to exert less effort for reward compared to non-deficit patients (Fervaha et al., 2015), and deficit schizophrenia has been associated with decreased activation of the dorsal caudate in response to reward anticipation compared to non-deficit patients and healthy controls (Mucci et al., 2015). Thus, targeting the immune system with cytokine antagonists may be a future treatment option for individuals with increased inflammation and deficit schizophrenia or persistent negative symptoms (Miller and Buckley, 2017).

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Figure 1.

a) Mean (SD) concentrations of tumor necrosis factor (TNF)-α in study groups. *- significantly different from Non-deficit and Control ($p < 0.05$) b) Partial regression plot of the relationship between ln tumor necrosis factor (TNF)-α and PANSS Negative Scale Score in all patients with schizophrenia, controlling for race and CPZ equivalents

Table 1

Sociodemographic, Clinical and Immunological Characteristics of the Sample

Variable	Schizophrenia		Controls (n=28)	p-value [^]
	Deficit (n=17)	Non-Deficit (n=39)		
Age, mean (SD)	44.7 (10.7)	40.9 (12.9)	39.8 (13.5)	0.440
Sex	7M; 10F	22M; 17F	13M; 15F	0.517
Race, % Caucasian	5.9%	35.9%	46.4%	0.027
Education, % HS graduate	47.1%	38.5%	78.6%	0.004
% Never Married	70.6%	43.6%	35.7%	0.053
BMI, mean (SD)	33.6 (7.0)	31.3 (7.6)	29.2 (5.5)	0.113
Cigarettes/day, mean (SD)	7.0 (9.7)	7.9 (9.6)	1.1 (3.4)	0.003
CPZ Equivalents, mean (SD)	577 (666)	334.2 (381.3)		0.090
PANSS Positive, mean (SD)	16.1 (5.1)	20.1 (6.6)		0.031
PANSS Negative, mean (SD)	19.1 (6.2)	14.6 (4.7)		0.004
PANSS General, mean (SD)	29.4 (8.2)	38.1 (8.8)		0.001
PANSS Total, mean (SD)	64.5 (16.5)	72.7 (16.5)		0.094
PANSS Disorganized, mean (SD)	2.0 (1.4)	1.9 (1.3)		0.839
PANSS Depression, mean (SD)	1.5 (1.1)	3.1 (1.6)		0.000
IFN- γ^a , mean (SD) pg/ml	5.6 (9.4)	5.3 (9.8)	2.6 (3.0)	0.461
IL-1 β^b , mean (SD) pg/ml	26.6 (32.4)	9.3 (6.9)	29.1 (93.1)	0.333
IL-6 ^c , mean (SD) pg/ml	14.9 (30.1)	5.3 (3.6)	10.8 (27.0)	0.240
sIL-2R ^c , mean (SD) pg/ml	168.8(152.5)	138.4 (110.5)	119.2 (67.0)	0.363
TNF- α^c , mean (SD) pg/ml	14.0 (11.5)	5.1 (2.5)	6.1 (4.9)	0.000

[^] p values represent level of significance of comparisons among groups using chi-square, t-test, or one-way analysis of variance where appropriate

^a Non-deficit schizophrenia n = 34; Controls = 19

^b Non-deficit schizophrenia n = 34; Controls n = 22

^c Controls n = 25