Review Article

Cytokines in Schizophrenia: Hope or Hype?

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ABSTRACT

Although there is a cumulative evidence for the inflammation pathophysiology in schizophrenia, it has not been conclusively proven yet. One reason for this is the lack of studies that have controlled for major confounding factors such as obesity, smoking, antipsychotic use, and stress. The studies in which the major confounding factors were controlled were done in subjects in acute relapse and in treatment-resistant schizophrenia. To date, no studies have been done in stable outpatients with schizophrenia controlling for major confounding factors. Data on cerebrospinal fluid cytokines in large sample independent of confounding factors are also lacking. The efficacy signal from anti-inflammatory medications in schizophrenia has been modest. In this study, the inconsistent and nonvalidated cytokine findings independent of the confounding factors are discussed.

Key words: *Confounding factors, cytokines, schizophrenia*

INTRODUCTION

Although there is a cumulative evidence for the inflammation pathophysiology in schizophrenia, it has not been conclusively proven yet. One reason for this is the lack of studies that have controlled for major confounding factors such as obesity, smoking, antipsychotic use, and stress.[1,2] Of the 83 schizophrenia studies included in the meta-analyses,[1,2] only three studies controlled for smoking[3-5] and only two studies controlled for both body mass index (BMI) and smoking.[6,7] The purpose of this review study is to highlight the inconsistent and nonvalidated cytokine findings independent of the confounding factors mentioned above.

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ARE CYTOKINE ABNORMALITIES INDEPENDENT OF POTENTIAL CONFOUNDING FACTORS?

Multiple factors modify cytokine concentrations including age, gender, infection, cancer, trauma, rheumatologic diseases, metabolic syndrome, obesity, and smoking. In women, use of oral contraceptives, menopausal status, and hormone replacement therapy can affect cytokine concentration.[8] Studies have consistently demonstrated that African-Americans and Hispanics have higher levels of inflammatory markers than the whites.[9,10] Socioeconomic status (SES) is associated with inflammatory state. People from lower

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SES have higher levels of inflammatory biomarkers.[11-13] Most of the people with schizophrenia have low SES. Exercise can impact inflammatory cytokines.[14] Diet[15,16] including caffeine intake[17,18] can affect cytokine concentrations. Insomnia, common in people with schizophrenia, is associated with abnormal cytokine concentrations.[19] Medications commonly prescribed for people with schizophrenia including but not limited to selective serotonin reuptake inhibitors,[8,20] aspirin,[21] statins,[22] and antihypertensives[23] influence cytokines.

CYTOKINES INDEPENDENT OF SMOKING

Serum interleukin (IL)-6, IL-1 receptor antagonist (RA), IL-8, and IL-10 in participants with schizophrenia (n = 31) were significantly different compared to controls (n = 7) even after controlling for smoking. This study was done in participants with treatment-resistant schizophrenia.[4,5] IL-12 level did not differ between smokers (n = 32) and nonsmokers (n = 24) in 56 drug-naïve participants with first episode psychosis in acute relapse.[3]

CYTOKINES INDEPENDENT OF BODY MASS INDEX AND SMOKING

In 361 in patients with psychiatric diagnoses (schizophrenia n = 59, schizoaffective disorder n = 29), there were no significant differences in IL-1RA, soluble IL-2 receptor (sIL-2R), soluble tumor necrosis factor-receptor (sTNF-R), p75, and IL-6 compared to 64 controls after controlling for age, gender, BMI, smoking, ongoing or recent infectious diseases, or prior medications.[6] This study was done in patients who were in acute relapse.

CYTOKINES IN SCHIZOPHRENIA IN ANTIPSYCHOTIC-NAÏVE SUBJECTS

IL-2 and interferon-gamma (IFN-γ) were not significantly different in 10 antipsychotic-naïve participants with schizophrenia compared to 15 controls.[24] In 12 participants with schizophrenia who were antipsychotic-naïve, sIL-2R was significantly elevated compared to 14 controls.[25] TNF-α and serum neopterin were not significantly different in 23 antipsychotic-naïve participants with schizophrenia compared to 16 controls.[26] In 14 antipsychotic-naïve participants with schizophrenia, IL-1RA was significantly higher and Clara cell protein 16 was significantly lower compared to 30 controls.[27] In 26 participants with schizophrenia who were antipsychotic-naïve, IL-2sRα, IL-6, and IL-1RA concentrations were higher compared to 27 controls.[28] In 25 antipsychotic-free male participants with schizophrenia who were in acute relapse, IL-2 and homovanillic acid were significantly higher compared to 25 controls.[29] IL-2 was significantly lower and IL-1β and TNF-α were significantly higher in 53 antipsychotic-naïve participants with schizophrenia compared to 62 controls.[30] In 88 participants with schizophrenia who were antipsychotic-naïve or antipsychotic-free for 4 months, IFN-γ and transforming growth factor beta 1 were significantly higher and IL-4 was significantly lower compared to 88 controls.[31] In another study with 56 participants who were antipsychotic-naïve, IL-12 concentrations were higher compared to 28 controls.[3] In 71 participants with schizophrenia who were antipsychotic-naïve or antipsychotic-free for 4 months, IFN-γ, TNF-α, and IL-6 were significantly higher, IL-2 and IL-4 significantly lower compared to 174 controls.[32] Finally, blood mononuclear cells mRNA expressions of IL-1β and TNF-α were significantly higher in 83 antipsychotic-naïve participants with first episode schizophrenia compared to 65 controls.[33]

CYTOKINES IN ANTIPSYCHOTIC-NAÏVE SCHIZOPHRENIA INDEPENDENT OF BODY MASS INDEX AND SMOKING

In 34 drug-free participants with schizophrenia with acute exacerbation, IL-1β, sIL-2R, IL-6, IL-8, and TNF-α concentrations adjusted for age, gender, BMI, and smoking were not different compared to 23 controls.[34] In 50 participants (schizophrenia n = 35), with a recent diagnosis of nonaffective psychosis who were antipsychotic-naïve, IL-6 concentration was significantly higher compared to 50 controls. This finding is also independent of BMI and smoking. This study was done in participants who were in acute relapse.[7] In deficit schizophrenia (n = 20), IL-6 and C-reactive protein concentrations were significantly higher compared to nondeficit schizophrenia (n = 42) in newly diagnosed participants with nonaffective psychosis who were antipsychotic-naïve.[35] Cytokines in 180 antipsychotic-naïve first episode schizophrenia participants were compared to 350 controls matched for potential confounding factors including age, sex, smoking, and BMI. Of nine cytokines (IL-1α, IL-1RA, IL-5, IL-10, IL-12p40, IL-15, IL-18, IFN-γ, and TNF-α), the concentrations of IL-1RA, IL-10, and IL-15 were increased significantly in participants with schizophrenia. The changes in IL-10 levels on antipsychotic treatment were significantly correlated with the improvements in symptoms. This suggests that both pro- and anti-inflammatory cytokines may be altered in people with first episode psychosis.[36]

MODEST ANTI-INFLAMMATORY TREATMENT RESPONSE

A review of 26 double-blind randomized controlled trials (RCTs) in schizophrenia looked at the anti-inflammatory effects of the following medications: Aspirin, celecoxib, davunetide, and fatty acids such as eicosapentaenoic acids and docosahexaenoic acids, estrogens, minocycline, and N-acetylcysteine (NAC). Of these, aspirin, estrogens, and NAC had a modest effect size of 0.3, 0.5, and 0.45, respectively. Celecoxib, minocycline, davunetide, and fatty acids showed no significant effect.[37] In a meta-analysis of eight RCTs (n = 774), adjunctive nonsteroidal anti-inflammatory drugs for schizophrenia had only a minimal benefit in positive symptoms in participants on antipsychotics.[38] In an RCT published recently, the effect of minocycline (n = 29) on the MATRICS Consensus Cognitive Battery composite score and positive symptoms were not statistically significant compared to 23 participants on placebo.[39] There are two ongoing studies with tocilizumab in schizophrenia (NCT01696929, NCT02034474).

Taken together, the evidence for the inflammation hypothesis is not compelling despite all the studies that have controlled for the confounding factors coupled with the modest anti-inflammatory treatment response. To date, no studies have been done in stable outpatients with schizophrenia controlling for major confounding factors. Furthermore, studies are also limited by small sample sizes and other methodological issues[40,41] to draw any firm conclusions.

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Conflicts of interest
There are no conflicts of interest.

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