Inflammation in Schizophrenia: Cytokine Levels and Their Relationships to Demographic and Clinical Variables

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Objective: *Inflammation may play a role in the accelerated physical aging reported in schizophrenia, though biomarker findings and associations with demographic and clinical factors are inconsistent.* **Methods:** *In a cross-sectional, case-control design, 95 outpatients with schizophrenia (mean age ± SD: 48.1 ± 10.2 years) and 95 demographically comparable healthy comparison subjects (HCs) (mean age ± SD: 48.1 ± 12.1 years) were studied. Sociodemographic and clinical data were collected, and plasma levels of tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6) and interferon-γ (IFN-γ) were assayed. The authors compared cytokine levels, examined demographic and clinical associations, and adjusted for relevant variables with linear models.* **Results:** *Individuals with schizophrenia had higher levels of TNF-α and IL-6 but not IFN-γ than HCs. Age was not related to cytokine levels, and age relationships did not differ between diagnostic groups. Women had higher levels of IL-6. TNF-α and IL-6 levels were significantly correlated with depressive symptoms, and adjustment for depression reduced the group effect for both. Within the HCs, TNF-α levels were associated with physical comorbidity and body mass index. IL-6 levels were significantly correlated with body mass index and within schizophrenia patients, with worse mental and physical well-being. Accounting for physical morbidity and mental well-being reduced group differences in TNF-α and IL-6 levels, respectively. Worse positive symptoms were associated with higher IL-6 levels.* **Conclusion:** *Higher TNF-α and IL-6 levels in schizophrenia patients were associated with depression, physical comorbidity, and mental well-being. Further longitudinal studies are warranted to assess inflammation as a potential treatment target for a subgroup of schizophrenia.* (Am J Geriatr Psychiatry 2017; 25:50–61)

Key Words: TNF-α, IL-6, IFN-γ, schizophrenia, inflammation, cytokines

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INTRODUCTION

Schizophrenia, a serious mental illness, is also associated with increased physical morbidity and premature mortality,[1–7] possibly suggesting accelerated biologic aging.[8] This may stem from dysregulated inflammatory processes.[9,10] There is a large, but inconsistent, literature examining inflammatory blood-based markers in schizophrenia, including high-sensitivity C-reactive protein, interleukin-6 (IL-6), IL-6 receptor, and soluble IL-2 receptor.[11–17]

The present study focused on three inflammatory cytokines with well-characterized immunologic functions and evidence of a role in the central nervous system: tumor necrosis factor (TNF)-α, IL-6, and interferon (IFN)-γ. TNF-α has important roles in neurogenesis, neuronal cell death, and innate and adaptive immune response.[18] Studies on TNF-α vary from higher levels,[14,19–28] no difference,[29–39] to lower levels in schizophrenia.[40–44] IL-6 has proinflammatory and, under certain conditions, anti-inflammatory effects[45] and was elevated in nearly two-thirds of published reports,[14,21,23,27,28,34–38,43,46–61] no different in one-third,[19,20,22,25,29–31,33,44,62–66] and lower in schizophrenia in one study.[67] IFN-γ is involved in lymphocyte activation and the kynurenine pathway of tryptophan metabolism, which may link inflammatory processes with glutamatergic and dopaminergic systems. Nine studies of IFN-γ reported lower levels,[23,43,68–74] four found higher levels,[28,36,75,76] and six showed no difference in levels.[37,66,77–80]

Age is a crucial factor because chronic elevation of inflammatory cytokine levels may indicate immunosenescence, because highly differentiated ("aged") immune cells readily produce inflammatory molecules. Normal aging affects central nervous system regeneration and repair processes, including dysregulation of TNF-α and IL-6.[81] TNF-α, IL-6, and IFN-γ blood levels have been shown to vary with age in healthy samples,[23,60,80,82] although findings in schizophrenia are mixed; with only one study of TNF-α levels,[80] three studies of IL-6,[23,60,80,82] and one study of IFN-γ[14,20,38,43,44,46,51,54] finding significant correlations between age and cytokine levels only in persons with schizophrenia. Although these findings are somewhat suggestive of a stronger correlation of age with cytokine levels in persons with schizophrenia than healthy comparison subjects (HCs), none of these studies directly compared the magnitude and direction of the correlations between those groups. It is important to compare the apparent rate of aging between patients and HCs to understand if there is an accelerated trajectory of inflammatory aging. In a cross-sectional study, one possible indication of this would be a statistically stronger association with age in persons with schizophrenia compared with the HC group, previously not shown for these three cytokines.

Gender is another potentially important factor in understanding group differences in cytokine levels. TNF-α levels have been reported to be higher in women than in men, both in the general population[83] and in schizophrenia.[84] IL-6 levels[83,85] have been reported to be higher in women compared with men in the general population, although the opposite relationship was seen in persons with schizophrenia.[60] Because of the unclear relationship between gender, diagnosis, and cytokine levels, careful gender matching is needed when examining diagnostic group differences, and it is important to explore further possible interactions between gender and diagnosis. Finally, studies in persons with cardiovascular disease have demonstrated that cytokine levels (specifically, IL-6) vary significantly by race,[60,83] suggesting the need for well-matched samples based on racial/ethnic composition.

Previous studies are inconsistent in the degree to which patient groups are matched on demographic factors, the exploration of possible associations with age and gender, and examination of whether such associations differ among people with schizophrenia. Furthermore, there is often little consideration of whether group differences in inflammatory markers persist after adjusting for the myriad of potentially related factors (e.g., body mass index [BMI], smoking, depression, physical illnesses, anti-inflammatory medication) that often differ between persons with schizophrenia and HCs. In most cases, it is not possible to create matched groups for a long list of covariates without severely limiting the generalizability of the sample. One can explore whether adjusting for them reduces the magnitude of the diagnostic difference in cytokine levels. In the current analysis, we defined potential confounds as those variables that (1) differed significantly between persons with schizophrenia and HCs in our sample and (2) were correlated with either cytokine level in either group. We then examined for each potential confounder whether group differences in cytokine levels persisted after statisti-