Elevated Serum Levels of High-Sensitivity C-Reactive Proteins Are Associated With Severe Delusional Symptoms in a Subgroup of Patients With Schizophrenia

To the Editor: Accumulating research evidence supports that inflammation and immunologic dysfunction may have a role in the etiology of psychotic disorders, including schizophrenia.[1] Cytokines, particularly interleukin 6 (IL-6) and IL-1β, are primary inducers of acute phase proteins including C-reactive protein (CRP).[2,3] We evaluated the levels of 38 cytokines and high-sensitivity CRP (hsCRP) in serum from 71 patients with schizophrenia (*DSM-IV*). We previously reported the correlation of inflammatory cytokines with positive symptoms in these subjects.[4] Here, we hypothesized that differential levels of CRP would be linked to distinct symptoms of psychopathology as measured by in the Positive and Negative Syndrome Scale[5] (PANSS) scores.

Method. Serum cytokines levels were measured with Millipore bead-based flow immunoassays (Millipore Corp) in a Luminex 100 system (Luminex Corp). Symptom severity in 71 schizophrenic subjects was evaluated using the PANSS.[5] The subjects were evaluated by using the total PANSS scores, general psychopathology scores, negative scale scores, positive scale scores, and the scores from the individual positive subscale PANSS symptoms: Delusions, Hallucinatory behavior, Suspiciousness/persecution, Conceptual disorganization, Excitement, Grandiosity, and Hostility. The levels of 38 cytokines at each visit were correlated with PANSS scores. The measurements of hsCRP were performed at the Veterans Affairs (VA) hospital in San Antonio, Texas, as part of standard of care. Levels of hsCRP above 0.9 mg/dL were flagged as high according to the reference range accepted at the VA clinical laboratory. All statistical analyses were performed using SAS Version 9.3 (SAS Institute Inc., Cary, NC). A *P* value of <.05 was considered to be statistically significant.

Results. All patients had a long-standing diagnosis of chronic paranoid schizophrenia and were under treatment with antipsychotic medications. We found 11 patients to have levels of hsCRP higher than 0.9 mg/dL. No significant differences in gender, ethnicity, body mass index, or weight were found between subjects with high CRP and those in the normal range (Table 1). No differences in levels of cholesterol, triglycerides, high-density lipoproteins, low-density lipoproteins, and blood counts (assessed at the VA hospital in San Antonio, Texas, as standard of care) were observed. Further, we found no differences in level of care at the time of psychiatric evaluation, smoking habits, comorbidity with posttraumatic stress disorder, or additional treatment with antidepressants (Table 1). The veterans with high levels of hsCRP had no physical signs of infection or exacerbation of medical or surgical problems. Overall, the elevated serum levels of hsCRP were associated with more severe psychopathology.

Table 1 also summarizes the results of association of high levels of hsCRP with psychopathology symptoms estimated by PANSS and multiple comparisons. In the group with high hsCRP, the scores for delusional symptoms were statistically higher compared with the normal-level group, with a *P* value of .0098 (the highest possible delusional score is 7). To our knowledge, this is the first report of levels of hsCRP positively correlated with specific measures of delusions. Previously it was reported that elevated CRP was a significant predictor of both PANSS total and negative symptoms.[6]

Table 1. Demographics and Clinical Characteristics of Veterans With Schizophrenia With Elevated Levels of High-Sensitivity C-Reactive Protein (hsCRP) vs Veterans With Schizophrenia With Normal Levels of hsCRP[a]

Characteristic	hsCRP High (n = 11)	hsCRP Normal (n = 60)	P Value
Age, y	51.1 ± 9.3	54.1 ± 10.5	.3998
Male	8 (72.7)	54 (90.0)	.1135
Ethnicity			.8046
White	4 (36.4)	28 (46.7)	
Black	2 (18.2)	10 (16.7)	
Hispanic	4 (36.4)	20 (33.3)	
Other	1 (9.1)	2 (3.3)	
BMI, kg/m^2	30.9 ± 4.6	30.4 ± 5.8	.7559
Smoker	8 (72.7)	38 (63.3)	.7356
Cholesterol, mg/dL			
Total	145.2 ± 37.1	166.9 ± 42.0	.1141
HDL	45.2 ± 14.4	53.2 ± 50.4	.3108
LDL	67.3 ± 25.2	91.7 ± 30.9	**.0161**
Triglycerides, mg/dL	147.8 ± 80.1	163.5 ± 138.3	.7415
Increased lymphocytes	2 (18.2)	11 (18.3)	1.0000
Increased neutrophils	2 (18.2)	5 (8.3)	.2955
Increased monocytes	4 (36.4)	9 (15.0)	.1077
Increased eosinophils	2 (18.2)	1 (1.7)	.0606
Increased basophils	2 (18.2)	5 (8.3)	.2955
Acute care	2 (18.2)	3 (5.0)	.1685
PTSD	1 (9.1)	7 (11.7)	1.0000
Substance use history	5 (45.5)	30 (50.0)	.7816
Antidepressant	5 (45.5)	24 (40.0)	.7351
PANSS total score higher than 100	4 (36.4)	10 (16.7)	.2093
PANSS Score			
Delusions	5.27 ± 1.95	3.72 ± 1.76	**.0098**
Hallucinatory behavior	3.27 ± 2.15	3.28 ± 1.91	.9868
Suspiciousness/persecution	4.00 ± 1.84	3.37 ± 1.56	.2333
Conceptual disorganization	3.64 ± 1.91	3.37 ± 1.46	.5938
Excitement	2.09 ± 1.14	2.12 ± 1.08	.9425
Grandiosity	2.64 ± 1.69	2.23 ± 1.90	.5133
Hostility	1.45 ± 0.82	1.47 ± 0.95	.9684
Positive scale score	23.27 ± 7.52	21.20 ± 8.63	.4586
Negative scale score	24.82 ± 8.21	21.35 ± 6.66	.1302
General psychopathology	41.27 ± 13.97	40.75 ± 11.73	.8954
Total PANSS score	89.00 ± 24.59	82.75 ± 24.16	.4342

[a]Values represent mean ± SD or n (%). Bolded values represent statistical significance.
Abbreviations: BMI = body mass index, HDL = high-density lipoproteins, LDL = low-density lipoproteins, PANSS = Positive and Negative Syndrome Scale, PTSD = posttraumatic stress disorder.

In another study,[7] elevated levels of CRP were associated with more severe cognitive symptoms.

Conclusions and Relevance. This study is limited to testing a pragmatic hypothesis that hsCRP would correlate with severity of psychopathology. It does not accurately estimate potential confounders such as the relationship of hsCRP to cardiovascular disease, and it does not address the molecular mechanisms leading to the observed association with delusions. Our study is also limited by the small sample size and the necessity of adjusting for multiple comparisons. However, our results suggest that measurements of hsCRP may be useful for the clinical care of patients with schizophrenia, in terms of treatment of psychotic symptoms.

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