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Total and differential white blood cell counts, high-sensitivity C-reactive protein, and cardiovascular risk in non-affective psychoses

Brian J. Miller [a,*], Prianka Kandhal [b], Mark Hyman Rapaport [c], Andrew Mellor [d], Peter Buckley [b]

[a] Department of Psychiatry and Health Behavior, Georgia Regents University, Augusta, GA, United States
[b] Medical College of Georgia, Georgia Regents University, Augusta, GA, United States
[c] Department of Psychiatry and Behavioral Sciences, Emory University, Atlanta, GA, United States
[d] Cancer Immunology, Inflammation and Tolerance Program, Georgia Regents University, Augusta, GA, United States

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ABSTRACT

Schizophrenia is associated with increased cardiovascular disease morbidity and mortality. Schizophrenia is also associated with immune and inflammatory abnormalities, including aberrant blood levels of lymphocytes, cytokines and high-sensitivity C-reactive protein (hsCRP). The purpose of this study is to investigate the relationship between total and differential white blood cell (WBC) counts, hsCRP, and indices of cardiovascular disease risk in patients with schizophrenia and related non-affective psychoses. 108 inpatients and outpatients age 18–70 with non-affective psychoses and 44 controls participated in this cross-sectional study. Subjects had a fasting blood draw between 8 and 9 am for glucose, lipids, total and differential WBC counts, and hsCRP. Vital signs and medical history were obtained. Patients with non-affective psychosis had significantly higher hsCRP levels than controls ($p = 0.04$). In linear regression analyses, lymphocyte and monocyte counts were a significant predictor of the total-to-HDL cholesterol ratio in subjects with non-affective psychosis ($p \leqslant 0.02$ for each). In binary logistic regression analyses, total WBC count was a significant predictor of an elevated 10-year estimated risk of myocardial infarction and cardiovascular disease in subjects with non-affective psychosis ($p \leqslant 0.03$ for each). Associations between total and differential WBC counts and cardiovascular disease risk indices were stronger in males than females with non-affective psychosis. Our findings provide further evidence that measurement of total and differential WBC counts may be germane to the clinical care of patients with schizophrenia and related disorders, and support an association between inflammation and cardiovascular disease risk in these patients.

1. Introduction

Cardiovascular disease is the leading cause of death in patients with schizophrenia and related disorders, and premature mortality is dramatically increased in this patient population (Brown, 1997; Harris and Barraclough, 1998; Miller et al., 2006; Saha et al., 2007). A number of different assessment tools have been developed to predict cardiovascular disease risk in the general population, including the Framingham Risk Score (FRS), the Framingham General Cardiovascular Risk Score (FGRS), and the total-to-HDL cholesterol ratio. The FRS is a tool for estimating the 10-year risk of having a myocardial infarction (Wilson et al., 1998), and incorporates data on age, sex, total and HDL cholesterol, systolic blood pressure, smoking status and current anti-hypertensive medication. The FGRS is a tool for estimating the 10-year risk of all cardiovascular disease events (including coronary, cerebrovascular, and peripheral arterial disease and heart failure), and is comprised of the same variables as the FRS, plus the presence or absence of diabetes (D'Agostino et al., 2008). The total-to-HDL cholesterol ratio is also used as a predictor of cardiovascular disease risk (Conroy et al., 2003; Lemieux et al., 2001).

In a survey of 102 subjects with schizophrenia, McCreadie et al. (2003) found a 53% prevalence of an elevated total-to-HDL cholesterol ratio (defined as >5.0). Several previous studies have also found increased FGRS in patients with schizophrenia compared to controls (Jin et al., 2011; Ratliff et al., 2013; Said et al., 2012; Sicras-Mainar et al., 2013; Tay et al., 2013; Wysokinski et al., 2012; Yazici et al., 2011). Among 689 subjects from the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) and

* Corresponding author at: Department of Psychiatry and Health Behavior, Georgia Regents University, 997 Saint Sebastian Way, Augusta, GA 30912, United States. Tel.: +1 706 721 4445; fax: +1 706 721 1793.
E-mail address: brmiller@gru.edu (B.J. Miller).

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matched controls from the National Health and Nutrition Examination Survey III, mean FGRS scores were significantly elevated in both males (9.4% vs. 7.0%) and females (6.3% vs. 4.2%) with schizophrenia (Goff et al., 2005). In several studies, presence of the metabolic syndrome was associated with increased cardiovascular disease risk (Said et al., 2012; Tay et al., 2013; Wysokinski et al., 2012; Yazici et al., 2011).

The metabolic syndrome is a constellation of metabolic risk factors associated with the development of atherosclerotic cardiovascular disease (Galassi et al., 2006; Grundy et al., 2005) and cardiovascular disease mortality (Galassi et al., 2006). The metabolic syndrome is common in patients with schizophrenia and related disorders, with a prevalence of 43%—based on American Heart Association criteria (Grundy et al., 2005)—in the CATIE trial (McEvoy et al., 2005). The metabolic syndrome is also associated with a state of chronic, low-grade inflammation (Devaraj et al., 2010). A meta-analysis found that the acute phase inflammatory marker high-sensitivity CRP (hsCRP) was an independent predictor of cardiovascular disease (Kaptoge et al., 2010). Schizophrenia is also associated with immune and inflammatory abnormalities, including aberrant blood levels of lymphocytes (Miller et al., 2013a,b), cytokines (Miller et al., 2011) and hsCRP (Miller et al., 2014), including studies in patients with first-episode psychosis and minimal exposure to antipsychotics. The adverse effects of atypical antipsychotics further impact risk of the metabolic syndrome, and subsequently, cardiovascular disease risk in patients with schizophrenia.

Total and differential white blood cell (WBC) counts and hsCRP blood levels may predict metabolic syndrome in patients with schizophrenia and other non-affective psychoses (Fan et al., 2010; Miller et al., 2013b). Another recent study found that in patients with schizophrenia, CRP levels were linearly associated with 10-year cardiovascular disease risk (stratified by low, moderate, and high/very high; Sicras-Mainar et al., 2013). However, total and differential WBC counts have not been explored as a predictor of cardiovascular disease risk in schizophrenia. The purpose of the present study, therefore, is to investigate the relationship between total and differential WBC counts, hsCRP, and indices of cardiovascular disease risk in patients with schizophrenia and related non-affective psychoses. We hypothesize that these measures are associated with increased cardiovascular disease risk in subjects with non-affective psychosis.

2. Methods

2.1. Subjects

108 inpatients and outpatients aged 18–70 and diagnosed with schizophrenia ($n = 66$) and related non-affective psychoses, including schizoaffective disorder ($n = 39$), psychotic disorder not otherwise specified ($n = 2$), or brief psychotic disorder ($n = 1$), and forty-four controls, who were part of studies of immune function in schizophrenia and related disorders, were recruited in the Augusta, Georgia area between July 2010 and June 2014. The broader category of non-affective psychosis, which includes schizoaffective disorder, appears to share characteristics of schizophrenia (Lichtermann et al., 2000; Tamminga et al., 2013). Recruitment was non-randomized. Subjects were referred to the investigators by their inpatient or outpatient psychiatrist. Exclusion criteria for all subjects for the present study included alcohol withdrawal; pregnancy; current scheduled use of non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids, or other immunomodulatory agents; history of exposure to an antibiotic in the past 2 weeks (based on subject's self-report plus a review of their electronic medical record); history of an immune disorder; current urinary tract infection; and illicit drug use in the past 30 days. "As needed" use of NSAIDs was not an exclusion criterion, although only one subject endorsed such use. No subject had a history of recent trauma or surgical intervention. All subjects had a negative urine drug screen. An additional exclusion criterion for patients was current use of clozapine. Additional exclusion criteria for controls were lifetime diagnosis of schizophrenia or related disorder; lifetime or current diagnosis of a manic, depressed, or mixed affective episode, or history of exposure to an antipsychotic, antidepressant, valproate, lithium or gabapentin. Antipsychotic medications were not standardized for subjects with non-affective psychoses. The majority of patients were treated with monotherapy with second-generation antipsychotics.

2.2. Procedures

After providing written informed consent, subjects underwent a laboratory, physical, and psychiatric diagnostic evaluation. Subjects had a blood draw between 8 and 9 am after a ten-hour fast. Vital signs, height/weight, and medical history were obtained. Diagnosis (or absence of a diagnosis in the controls) was verified using the Structured Clinical Interview for DSM-IV disorders (SCID) psychosis and mood disorders modules (Fennig et al., 1994). One rater (BJM) performed the SCID interviews. For patients, symptoms were assessed using the Positive and Negative Syndrome Scale (PANSS). A total of four raters performed the PANSS interviews for subjects in this study, although one rater (BJM) performed the majority of the interviews ($n = 83$, 77%). All raters were trained to perform the SCID and PANSS and inter-rater reliability with the principal investigator. Data on smoking (number of cigarettes per day) and other substance use was obtained using the Dartmouth Assessment of Lifestyle Inventory (DALI; Ford, 2003). Data on socioeconomic status (SES) was obtained using the Hollingshead-Redlich Scale (Hollingshead and Redlich, 1958). Data on current antipsychotic medications were used to calculate the subject's current daily dose in chlorpromazine (CPZ) equivalents (Woods, 2003, 2011). The study was approved by the IRB's of both Georgia Regents University and the Georgia Department of Community Health.

2.3. Laboratory evaluation

Blood analyses were performed at Clinical Pathology Laboratories Southeast (Augusta, Georgia). Complete blood counts with differential, fasting serum glucose, and lipid panels were analyzed by standard clinical laboratory assays. Glucose and lipids were measured using an Olympus AU2700 Chemistry-Immuno Analyzer (Olympus America, Inc., Melville, NY). CBC with differential was analyzed using a COULTER LH 750 Hematology Analyzer (Beckman Coulter, Inc., Brea, CA). hsCRP levels were measured using an enzyme-linked immunosorbent assay.

2.4. Indices of cardiovascular disease risk

The FRS was calculated using the National Heart, Lung, and Blood Institute tool for estimating 10-year risk of having a myocardial infarction (Wilson et al., 1998). The FGRS was calculated using the tool developed by D'Agostino et al. (2008) for estimating 10-year risk of cardiovascular disease events. The total-to-HDL cholesterol ratio was calculated by dividing total cholesterol by HDL cholesterol.

2.5. Statistical analysis

The data were analyzed using SPSS version 22 (SPSS, Inc.; Chicago, Illinois). Patients with non-affective psychoses and controls