European Psychiatry 31 (2016) 8–12

Contents lists available at ScienceDirect

European Psychiatry

journal homepage: http://www.europsy-journal.com

Original article

Elevated C-reactive protein levels in schizophrenia inpatients is associated with aggressive behavior

R. Barzilay [a,b,*], T. Lobel [a], A. Krivoy [a], D. Shlosberg [a], A. Weizman [a], N. Katz [a]

[a] Geha Mental Health Center, Sackler Faculty of Medicine, Tel Aviv University, 1 Helsinki St., 4910002 Petah-Tikva, Israel
[b] Neurosciences laboratory, Felsenstein Medical Research Center, Sackler Faculty of Medicine, Tel Aviv University, Israel

ARTICLE INFO

Article history:
Received 17 August 2015
Received in revised form 28 September 2015
Accepted 29 September 2015
Available online 3 December 2015

Keywords:
Schizophrenia
Inflammation
C-reactive protein
Aggression
Suicidal behavior
Neutrophil to lymphocyte ratio

ABSTRACT

Background: An association between inflammation and behavioral domains of mental disorders is of growing interest. Recent studies reported an association between aggression and inflammation. In this study, we investigated the association between aggressive behavior and inflammatory markers in schizophrenia inpatients.

Methods: Adult schizophrenia inpatients without affective symptoms ($n = 213$) were retrospectively identified and categorized according to their C-reactive protein measurement at admission as either elevated (CRP > 1 mg/dL; $n = 57$) or normal (CRP < 1 mg/dL; $n = 156$). The following indicators of aggression were compared: PANSS excitement component (PANSS-EC), restraints and suicidal behavior during hospitalization. Univariate comparisons between elevated and normal CRP levels were performed and multivariate analysis was conducted to control for relevant covariates.

Results: CRP levels significantly correlated with other laboratory markers indicating increased inflammation including leukocyte count and neutrophil to lymphocyte ratio ($r = 0.387$, $P < 0.0001$ and $r = 0.356$, $P < 0.0001$) respectively. Inpatients with elevated C-reactive protein displayed increased aggressive behavior compared to patients with normal CRP levels (<1 mg/dL). This was manifested by higher rates of restraint during hospitalization ($\chi^2 = 5.22$, P = 0.031) and increased PANSS-EC score (U = 5410.5, $P = 0.012$). Elevated CRP levels were not associated with suicidal behavior. Multivariate analysis revealed that higher PANSS-EC score was associated with elevated CRP after controlling for the covariates age, sex, BMI and smoking.

Conclusion: This study identified a potential biological correlate (inflammation) of a specific behavioral endophenotype (aggression) in schizophrenia inpatients.

1. Introduction

Schizophrenia inpatients often present with aggressive behavior during hospitalization, partly due to the association between positive symptoms and aggression [1,2]. Early identification and treatment of aggressive tendencies upon admission to a psychiatric facility may reduce the risk of patient and staff injury. Risk factors for aggression in schizophrenia patients include active psychosis, a history of aggressive behavior and illicit substance use [3]. These risk factors, however, are non-specific and the pursuit of other risk factors is an unmet need.

The role of inflammation in the underlying pathophysiology of aggressive behavior, both in healthy individuals [4] and in patients with psychiatric morbidity, has been recently investigated. Specifically, a positive correlation between aggression and serum and cerebrospinal fluid levels of the inflammatory marker C-reactive protein (CRP) was reported in patients with personality disorders and intermittent explosive disorder [5–7]. Suicidal behavior, as an expression of self-inflicted aggression, has also been found to correlate with increased inflammatory markers, both in cerebrospinal fluid [8] and in peripheral blood [9,10]. Elevated blood CRP levels were also reported in schizophrenia patients as compared to healthy controls [11], although studies evaluating the association of CRP levels with schizophrenia symptomatology have yielded inconclusive results, with some studies reporting correlation between CRP levels and certain clinical scales, while other report no such association [12–16].

To date, an association between aggressive behavior and inflammation in schizophrenia has not been investigated. This study, therefore, aimed to explore the relationship between aggressive behavior and elevated CRP levels in schizophrenia

* Corresponding author. Ran Barzilay, Geha Mental Health Center, Sackler Faculty of Medicine, Tel Aviv University, Israel. Tel.: +97 2523 020443; fax: +97 2775 251518.
E-mail address: barzilyr@post.tau.ac.il (R. Barzilay).

http://dx.doi.org/10.1016/j.eurpsy.2015.09.461
0924-9338/

inpatients. The association between clinical measures of aggression and suicidal behavior with CRP, a general laboratory marker of immune activation and inflammation, was retrospectively studied in schizophrenia patients admitted to a single closed ward.

2. Methods

2.1. Design

The study utilized a retrospective cross-sectional patients' records study design. Data was retrieved from the electronic medical records of all hospitalized patients between October 2010 and December 2013 in a single adult closed ward with a catchment area of approximately 300,000 inhabitants, at the Geha Mental Health Center (GMHC), a regional mental health center. The GMHC review board approved the study and waived the need for informed consent due to the retrospective nature of the study.

2.2. Subjects

Included in the study were all adult patients (n = 213, age 19–89) who were discharged with the primary psychiatric diagnosis of schizophrenia, based on the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV-TR) criteria. Patients diagnosed with a major affective disease (i.e. schizoaffective, bipolar disorder, major depression and mania) were excluded. We also excluded patients suffering from any acute physical illness, patients with fever (>37.9^{0}C) or those who were treated with antibiotics, steroids, antipyretics or anti-inflammatory medications.

2.3. Variables

Laboratory data associated with inflammation included blood tests routinely performed upon admission: white blood cells (WBC), platelets count, albumin levels and neutrophil to lymphocyte ratio [17]. CRP levels were determined in the ward as part of the routine laboratory tests conducted upon admission. Blood for CRP levels was drawn from all patients at 8 a.m within the first day after admission. Serum CRP levels were measured using Beckman Coulter AU 2700 analyzer (Brea, CA), by a particle enhanced immunoturbidimetric method, using latex particles coated with monoclonal anti-CRP antibodies (Roche CRPL3 reagent, Indianapolis, IN). The test is linear within a concentration range of 0.008–8 mg/dl. A level of >1 mg/dL was considered as elevated according to the classification of the American Heart Association and levels under 1 mg/dL were considered as normal [18]. All CRP levels were below 11 mg/dL, reducing the chance of an acute physical illness as a cause for the inflammatory state.

The clinical data retrieved included body mass index (BMI), smoking status (smoker or non-smoker, as documented at each admission following an interview by the admitting nurse), illicit substance use and treatment with antipsychotics as recorded upon admission. Psychiatric scales including the positive and negative syndrome scale (PANSS) [19] are routinely completed in GMHC. PANSS score was determined by the patient's treating psychiatrist following an interview that was conducted within 72 hours from admission as a routine practice of the inpatient unit. PANSS excitement component (PANSS-EC) was used as a measure of aggression and agitation [20–22]. The need for physical restraint during hospitalization and the presence of suicide ideation and/or suicide attempt at admission were recorded according to the evaluation of the medical records. Demographic and clinical characteristics of the sample are presented in Table 1.

Table 1
Demographic and clinical characteristics of the study subjects.

n = 213	
Age in years, mean (SD)	42.2 (14.09)
Sex	
Male, n (%)	133 (62.4)
Female, n (%)	80 (37.6)
BMI [kg/m^2]–mean (SD)	25.01 (5.17)
Smoking status	
Yes, *n* (%)	156 (73.2)
No, *n* (%)	57 (26.8)
Illicit substance use	
Cannabis use only, *n* (%)	21 (9.9)
Multiple substance use, *n* (%)	13 (6.1)
No illicit substance use, *n* (%)	179 (84)
Antipsychotics at admission	
Typicals, *n* (%)	99 (46.5)
Atypicals, *n* (%)	95 (44.6)
No pharmacotherapy, *n* (%)	19 (8.9)
Clinical measures	
PANSS total – mean (SD)	82.76 (22.8)
PANSS positive – mean (SD)	20.69 (6.89)
PANSS negative – mean (SD)	21.49 (7.46)
PANSS depression – mean (SD)	8.77 (3.79)

2.4. Statistical analysis

We used SPSS ver. 21 (SPSS Inc., Chicago, IL) for statistical analysis. Descriptive statistics are expressed as mean ± SD, or rate (%). Two groups of patients were compared by levels of CRP at the cutoff of 1 mg/dL (elevated vs. normal). For univariate analyses, we used 2-tailed Student's t-tests, Mann-Whitney U test or Chi-squared test as appropriate. Multivariate analysis was performed using binary logistic regression analyses with CRP levels (elevated or normal) as a dependent variable controlling for age, sex, BMI, smoking status and illicit substance use as covariates. A P-value < 0.05 was considered to indicate statistical significance.

3. Results

3.1. Increased CRP correlates with known laboratory inflammatory markers

CRP measurements were distributed in a non-normal manner with the majority of patients (156 from 213, 73.2%) below the mean (1.068 mg/dL, Fig. 1A). To validate the assumption that patients with an elevated CRP level (>1 mg/dL) present a subpopulation with increased inflammatory state, a correlation analyses was performed between CRP levels and other laboratory indices indicative of inflammation. We found that the following parameters significantly correlated with logCRP: albumin levels (Fig. 1B), platelets count (Fig. 1C), leukocytes count (Fig. 1D) and the neutrophil to lymphocyte ratio (Fig. 1E).

3.2. Elevated CRP is associated with increased aggressiveness

Clinical variables indicative of aggressive behavior, general measures based on the PANSS score, and evaluation of suicidal behavior, were compared between inpatients with normal and elevated levels of CRP. Covariates that could affect aggression and CRP levels including gender, age, BMI, illicit substance use and smoking status were compared. The results show that patients with elevated CRP levels are more aggressive during hospitalization as detected by statistically significant higher scores of irritability and aggressive behavior (PANSS-EC score), and by increased rates of physical restraint during hospitalization (Table 2). Noteworthy, we found no statistically significant differences in the other clinical measures, including suicidal behavior.