C-REACTIVE PROTEIN LEVEL AND ITS RELATIONSHIP WITH SUICIDE RISK AND ALEXITHYMIA AMONG NEWLY DIAGNOSED, DRUG-NAÏVE PATIENTS WITH NON-AFFECTIVE PSYCHOSIS

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The aim of the present study was to evaluate C-Reactive Protein (CRP) levels in newly diagnosed drug-naïve patients with non-affective psychosis, testing the hypotheses that in such patients serum CRP levels would be higher than in healthy controls and related to more severe psychopathology, suicide risk and alexithymia. CRP levels of 30 adult patients and 30 sex- and age-matched healthy controls were evaluated. Patients were tested with the Scale of Suicide Ideation (SSI), the Toronto Alexithymia Scale (TAS-20), the Scale for the Assessment of Positive and Negative Symptoms (SAPS and SANS) and the Calgary Depression Scale for Schizophrenia (CDSS). Higher suicide risk patients showed higher CRP levels than lower suicide risk patients and healthy controls. Moreover, such patients showed higher SAPS, SANS and CDSS scores than lower suicide risk patients. In linear regression model, CRP was significantly associated with higher SSI and TAS-20 scores. The results of the present study support the notion that CRP, suicide risk and alexithymia are strictly linked in newly diagnosed, drug-naïve patients with non-affective psychosis, independently of depressive symptoms or general psychopathology. Limitations are discussed.

Key words: C-reactive protein, suicide risk, alexithymia, depression, psychosis, drug-naive

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DISCLOSURE: ALL AUTHORS REPORT NO CONFLICTS OF INTEREST RELEVANT TO THIS ARTICLE.

The role of acute phase proteins in neuropsychiatric disorders has been widely investigated (1). Several studies have demonstrated an activation of the inflammatory response system and wide-ranging levels of cytokines in schizophrenia, particularly proinflammatory interleukins (ILs), which play an essential role in inflammation, being the major inducers of C-Reactive Protein (CRP), the prototypical protein up-regulated as part of the acute phase response in humans (2, 3). CRP is released almost exclusively in the liver by hepatocytes into the bloodstream any time there is active inflammation in the body (4). As reported by Eagan et al. (5), CRP serves as an activator of the complement system, an immunological pathway that supports the immune system by marking and removing non-self antigens. Activation of complement may contribute to the maintenance of the inflammatory response and is thought to be involved in neurodegenerative processes (5). Moreover, it is known that elevated CRP levels could be related to an increased risk for coronary heart disease (CHD), peripheral vascular disease, stroke and metabolic syndrome (6).

More recently, researchers' attention has been focused on interrelationships between CRP levels, depressive symptoms and suicide risk (7-8). Results indicate a possible association between higher CRP, severity of depressive symptoms and increased suicide risk at least in patients with affective disorders (9). Moreover, several studies have shown that alexithymia (a multifaceted construct that includes four different characteristics: (a) difficulty in identifying and describing feelings, (b) difficulty in distinguishing feelings from body sensations, (c) reduction in fantasy, and (d) concrete and poor introspective thinking) may be positively associated with a history of attempted suicide and increased suicide risk, especially in the presence of clinically relevant depressive symptoms (10).

However, to date, few studies have investigated the relationships between CRP levels and psychopathological status among patients with psychosis (11-12). In particular, to date, in literature no studies are present concerning the relationships between suicide risk, alexithymia and CRP in young patients at the first episode of psychosis who had never been exposed to antipsychotic treatment. Therefore, the aim of the present study was to evaluate CRP levels in patients with first episode of non-affective psychosis, testing the hypotheses that in drug-naïve patients serum CRP levels would be higher than in healthy controls and related to more severe psychopathology and higher suicide risk and alexithymia.

MATERIALS AND METHODS

Methods

Thirty adult patients (13 males and 17 females with a mean age of 25.9±6.0 years) with non-affective psychosis were recruited at the time of their first contact with psychiatric services and were evaluated before the administration of any antipsychotic pharmacotherapy.

The first episode psychosis patients met criteria for schizophrenia (n=25), schizophreniform disorder (n=2), brief psychotic disorder (n=1) and delusional disorder (n=2). Patients were diagnosed by clinical assessment, following the Structured Clinical Interview for DSM-IV (SCID; Italian version). Their average age was 25.3±4.2 years (age range: 19-35 years).

Exclusion criteria were age under 18 years or over 65 years, previous exposure to antipsychotic treatment, drug or alcohol dependence, organic mental disorders, pregnancy or nursing (women), treatment with anti-inflammatory or immunosuppressant drugs. Patients included in the study had no serious medical conditions in their history which required anti-inflammatory treatment. Endocrinologic disorders, diabetes, hypertension, liver dysfunction or other diseases necessitating chronic administration of drugs, abnormal concentrations of T3, T4, ALT, AST or proteinogram results were considered as exclusion criteria.

To assess suicide risk, the Scale of Suicide Ideation (SSI) scores (13), a rating scale with statements of suicidal intentions on a 3-point level, were evaluated. We employed the cut-off ≥ 6 to discriminate patients with higher suicide risk. Alexithymia was measured using the 20-item Toronto Alexithymia Scale (TAS-20), the most widely used measure of alexithymia (14). Pychopathology was evaluated with the Scale for the Assessment of Negative Symptoms (SANS) (15), the Scale for the Assessment of Positive Symptoms (SAPS) (17) and the Calgary Depression Scale for Schizophrenia (CDSS) (16). Self-reported weight and height was used to calculate Body Mass Index (BMI) (kg/m^2) and mean BMI of whole sample was 22.1±1.7 kg/m^2. A detailed questionnaire was used to collect information on smoking history from both patients and controls. Duration of untreated psychosis (DUP) was defined as the period in months between the first appearance of positive psychotic

symptoms and the day of inclusion in the study.

Serum CRP was measured using a highly sensitive nephelometric assay (BN-II Nephelometer; Dade Behring, Deerfield, IL, USA). This system was able to detect a minimal CRP concentration of 0.22 mg/dl. Blood samples were taken between 7:30 and 8:30 a.m. after the patients had fasted for at least 10 h. The profile of CRP levels of a control group of sex- and age-matched 30 normal subjects recruited from faculty and hospital staff was also evaluated.

Statistics

Descriptive statistics (means and standard deviations as appropriate) were computed for the study samples on demographic variables and other parameters. The differences between groups were tested by using analyses of covariance (ANCOVA) with suicide risk positivity/ negativity as factor and age, gender, BMI and smoking status as covariates. A model of linear regression with CRP as dependent variable and other variables (such as age, gender, BMI, smoking status, DUP, SAPS, SANS, CDSS, TAS-20 and SSI) as independent was conducted in order to assess potential relationships with CRP levels in the clinical sample. Two-tailed tests were used; P values equal or less than 0.05 were deemed statistically significant. Results are expressed as mean ± standard deviation (SD).

RESULTS

Prevalence of smokers in whole sample was 63.3% (n=19), whereas mean duration of untreated psychosis (DUP) was 8.7±3.4 months. Gender comparison between all demographic and clinical variables showed no significant differences. Prevalence of current suicide ideation (higher suicide risk, SSI scores ≥ 6) was 46.7% (n=14).

Mean CRP level in whole sample was 2.8±0.9 mg/liter. Comparison of CRP indicated that higher suicide risk patients showed higher CRP levels than lower suicide risk patients (respectively 3.5±0.6 *vs* 2.1±0.4, F=70.1 df=1 P<0.001). Both groups had higher CRP levels than normal controls (respectively 3.5±0.6 *vs* 1.5±0.6, F=101.2 df=1 P<0.001 and 2.1±0.4 *vs* 1.5±0.6, F=32.1 df=1 P<0.001) (Fig. 1).

Together with higher CRP levels, higher suicide risk patients showed higher SAPS, SANS and CDSS scores than lower suicide risk patients (Table I).

In the linear regression model (Table II), CRP was significantly associated with higher SSI and TAS-20 scores (for both P<0.001). In the current analyses, the r2 values accounted for 51% of the variance in CRP. In addition, the Durbin–Watson coefficient was 2.14 (near the optimum value of 2.0). A scatter plot of residuals and a plot of regression-standardized residuals indicated a near normal distribution.

DISCUSSION

To date, this was the first study that investigated the relationships between suicide risk, alexithymia and CRP in young patients at first episode of psychosis who had never been exposed to antipsychotic treatment. Two main points result from our study: i) patients with a current suicidal risk showed higher CRP levels and more severe psychopathology; ii) CRP was significantly associated with higher suicidal risk and alexythimia (2).

It is known that psychotic disorders such as schizophrenia and schizoaffective disorder may be associated with elevated CRP and it has been demonstrated that patients with higher CRP levels may have a more severe psychopathology and higher suicide risk (8, 17, 18). Recently, Fan et al. (17) investigated CRP levels in 26 subjects with psychosis and found that patients with elevated CRP levels also had significantly more severe psychiatric symptoms as measured by the total, negative and general psychopathology scales of the Positive and Negative Syndrome Scale. Moreover, in a study of 413 individuals with schizophrenia, Dickerson et al. (18) found that individuals with schizophrenia who had levels of CRP>=5.0 μg/ml had significantly lower cognitive scores than individuals with schizophrenia who did not have elevated CRP levels. Our findings seem to be consistent with such observations, confirming that higher CRP levels may be associated with higher disorder severity. On the other hand, other recent studies have not found elevated CRP in such patients (19, 20), but these studies have been carried out on patients treated with antipsychotics and it is known that antipsychotic medication use may be associated with elevated CRP due to metabolic changes (21, 22). Therefore, the strength of our study was that it was conducted on drug naïve patients, without previous treatments having a possible influence on the results.

Understanding the characteristics of suicide attempts in people with first episode psychosis may have implications for risk management at a

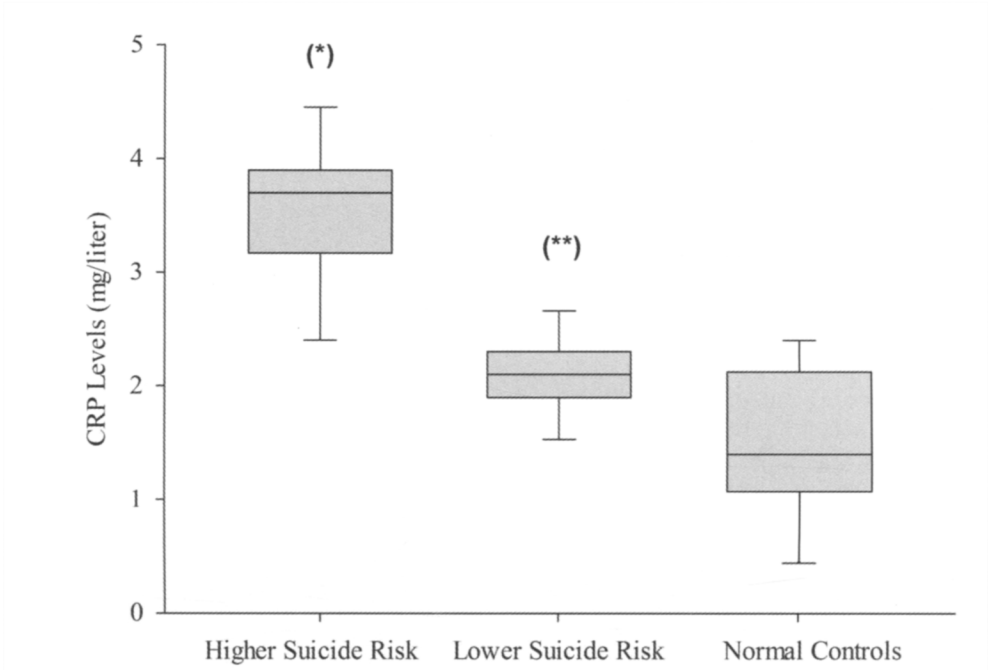

Fig. 1. *Boxplots of CRP levels among individuals with higher suicide risk (patients with SSI scores ≥ 6, n=14, 46.7%), lower suicide risk (patients with SSI ≤ 5, n=16, 53.3%) and sex- and age-matched normal controls. The solid line and short dash line indicate median and mean, respectively. The lower and upper boundary of box indicates 25th and 75th percentile, respectively. ANCOVA controlling for age, gender, BMI and smoking status. (*) P<0.001 vs lower suicide risk and normal controls (**) P<0.001 vs normal controls*

Table I. *Comparison of clinical data between individuals with higher (patients with SSI scores ≥ 6, n=14, 46.7%) and lower suicide risk (patients with SSI ≤ 5, n=16, 53.3%).*

	Higher suicide risk (SSI scores ≥ 6)	**Lower suicide risk (SSI scores ≤ 5)**	**Statistics**
DUP (months)	10±3.3	7.6±3.3	NS
SAPS	20.1±4.6	11.6±3.8	F=24.8 df=1, 29 P<0.001
SANS	15.9±5.5	10.3±5.2	F=5.5 df=1, 29 P=0.03
CDSS	9.1±1.1	3.9±2.2	F=57.5 df=1, 29 P<0.001
TAS-20	61.9±7.6	43.8±7.9	F=47.4 df=1, 29 P<0.001

ANCOVA controlling for age, gender, BMI and smoking status. Data are expressed as mean ± SD.

service level and local suicide prevention strategies (16). In our sample, 46.7% of patients (n=14) were categorized as having higher suicide risk. This is a considerable percentage in line with literature data and with the evidence that risk of suicidal behaviour is relatively high in such patients (21). The presence of alexithymia seems to be a further risk factor in patients with psychosis, therefore assessment of these patients should include evaluation of emotional responses as well as accurate investigation of

Table II. *Linear regression with CRP as dependent variables and age, gender, BMI, smoking status, DUP, SAPS, SANS, CDSS, TAS-20 and SSI as independent variables.*

Variables	Unstandardized Coefficients		Standardized Coefficients	t	P
	B	Std. Error	Beta		
(Constant)	1.768	0.217		8.132	<0.001
SSI	0.089	0.024	0.480	3.791	0.001
TAS-20	0.035	0.009	0.470	3.712	0.001

Only statistically significant variables are shown.
r^2=0.513 F=28.32 df=10 P<0.001

suicidal ideation (16). From a psychological and psychosocial point of view, this implicates that the presence of alexithymic traits may impair subjects with first episode psychosis more severely than non-alexithymic ones and therefore they must be almost immediately treated with adjunctive psychotherapy and rehabilitation interventions (22), in order to improve psychosocial functioning and minimize suicide risk, as it is known that pharmacotherapy does not substantially influence alexithymia per se (11).

It has been reported that higher CRP levels may be somewhat linked to alexithymia and increased suicide risk at least in patients with mood disorders (11, 12, 15). On the basis of the results of our study, this observation seems to be valid also for patients at first episode of psychosis. The finding of higher CRP levels associated with alexithymia may be consistent with the stress-alexithymia hypothesis (23): patients with more alexithymic features may be suffering from chronic stress reaction that, on its own, can promote transient and often subclinical increases in inflammatory factors such as CRP and ILs (15). Moreover, alexithymia is related to high cortisol levels due to short-term stress reactions, and cortisol may enhance the release of IL-6, the major inducer of CRP production by liver (8). In fact, higher cortisol levels have been found in schizophrenic patients with a violent suicidal attempt than in patients with non-violent attempts and healthy controls, suggesting that cortisol may be implicated in suicidality (24). Moreover, Pandey et al. (25) showed that the mRNA and protein expression levels of IL-6 were significantly increased in Brodmann area 10 (BA-10) of suicide victims compared with normal control subjects. Taken together, these findings suggest that, in patients at first episode of psychosis, the presence of alexithymia may be a condition characterized by higher cortisol levels leading to a pronounced and persistent inflammatory state, with higher circulating IL-6 levels that, on their own, may enhance CRP release. Higher CRP levels may act synergistically with higher cortisol and IL-6 levels reducing hippocampal volume and impairing monoaminergic transmission, thus favouring the development of depressive symptoms and suicidality (26). All considered, the results of our study support the potential use of CRP as biomarker to evaluate disorder severity and suicide risk, especially in alexithymic individuals.

The underlying mechanisms relating inflammation to psychosis are not yet fully elucidated. It has been reported that patients with psychosis show deficient regional blood flow in different brain areas, especially the frontal and temporal lobes, with decreased frontal blood flow associated with negative symptoms (19). Hanson and Gottesman (27) suggested that chronic inflammation might disrupt the micro-vascular system in the brain and impair the regulation of blood-brain barrier and cerebral blood flow. These modifications in homeostatic mechanisms of the brain might lead to the development of psychotic

symptoms. In addition, the neuropathology of psychosis has recently been reported to be closely associated with microglial activation that may contribute directly to the neuronal degeneration by producing CRP, several pro-inflammatory cytokines and free radicals (28).

This study has several limitations, and results should therefore be interpreted with caution. The first limitation is the relatively small sample size of patients: future studies should be conducted on larger samples in order to confirm our findings. Moreover, even if severity of psychosis and suicidal ideation were analysed using clinician-rated rating scales, alexithymia was assessed by a self-rated scale, with possible biases due to the inherent nature of self-rating scales: future studies should consider the use of clinician-rated measures of alexithymia. Finally, due to the cross-sectional design, our study lacks follow-up data. Definitive assessments of CRP, severity of the psychosis, mood states and alexithymia require that patients should be followed longitudinally, with serial CRP sampling as well after clinical remission and pharmacological treatment. Future studies should also consider the prospective assessment of both cortisol and IL-6 together with CRP, in order to fully elucidate the processes that may be the background of relationships between alexithymia, inflammation and suicide risk in patients at first episode of psychosis.

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