

The emerging role of C-reactive protein in affective and psychotic disorders

Il ruolo emergente della proteina C reattiva nei disturbi affettivi e psicotici

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Key words

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Summary

Background and objective

C-reactive protein is a pentameric protein which is generated in the liver and secreted in the blood to play a central role in inflammation. The measurement of C-reactive protein in the blood provides a reliable marker of chronic inflammation caused by infectious and other inflammatory agents. Increased levels of C-reactive protein have been associated with chronic infections and inflammatory conditions as well as with increased risk of inflammatory cardiovascular disorders. The aim of this review is to elucidate the current facts and views about C-reactive protein in psychiatric disorders such as major depression, bipolar disorder and schizophrenia.

Method

MedLine and PsycInfo/Embase databases were search using as key-

words C-reactive protein and each of DSM-IV mood and psychotic disorders to identify quality papers for reviewing.

Results

Several studies have examined the relationship between psychiatric disorders and C-reactive protein, but the majority of the studies in literature have been limited by retrospective, case-control study designs, and very few studies have examined the relationship between these disorders and C-reactive protein in large study samples (Tables I, III, IV).

Conclusion

In conclusion, the role of C-reactive protein in psychiatric disorders is, to date, intriguing, but somewhat unclear. Further prospective studies are needed to introduce C-reactive protein in clinical settings as a marker of psychopathological states.

Introduction

C-Reactive Protein (CRP), so called for its capacity to precipitate the somatic C-polysaccharide of *Streptococcus pneumoniae*^{1,2}, was the first acute phase protein ever described and quickly became a sensitive systemic marker of inflammation and tissue damage^{3,4}. The acute phase response is a non-specific physiological and biochemical response of endothermic animals to most forms of tissue damage, infection inflammation, malignant neoplasia and stroke^{5,6}. CRP is an acute-phase reactant that originates in the liver and has many pathophysiological roles in the inflammatory process.

CRP consistently has been associated with an increased risk of cardiovascular diseases, diabetes and other metabolic dysfunctions⁷⁻⁹. Recently, the availability of high sensitivity CRP test allowed to investigate more deeply the predictive relationship between CRP production and the coronary artery diseases¹⁰. Both in the primary and the secondary preven-

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tion settings, high sensitivity CRP assay can better target individuals at higher risk, thus improving outcomes and resulting in a more cost-effective strategy¹¹.

To date, as it is widely accepted that depression is a marker for the increased risk of subsequent coronary heart disease (CHD) and may be associated with an increased activation of the inflammatory system⁴⁷, this has suggested to some researchers to focus their attention on the possible interrelationships between CRP and mood disorders such as depression and bipolar disorder as well as schizophrenia. Therefore, the aim of this review was to elucidate the current facts and views about CRP in neuropsychiatric disorders such as major depression, bipolar disorder and schizophrenia.

Methods

Searches of the Medline database from 1988 through March 2009 and the PsycInfo/Embase database from 1988 through March 2009 were conducted with the helping of a professional librarian (M.C.), restricted to the English language. The search term "C-reactive protein" was combined with "depression", "depressive symptoms", "major depression", "bipolar disorder", "mania", "schizophrenia", "psychotic disorder", "psychosis", "delusions" and "hallucinations" to identify relevant original research and review articles. Bibliographies were scanned to locate additional relevant publications, even those older than 1988. Also articles in press were included, if available online. All citations were screened, and the full texts of peer-reviewed journal articles were obtained. However, not all articles on this topic were included in the paper and inclusion was limited to papers considered relevant for the purposes of the review, i.e. studies on large community samples of subjects, clinical investigations on patients with established DSM-IV diagnosis of major depression, bipolar disorder, schizophrenia and paper published on journal with relevant Impact Factor. Eligibility for inclusion was independently determined by all of the authors. Studies on chronic disease populations were excluded (e.g., end-stage renal disease or patients with cancer).

C-reactive protein and depression

Several studies have investigated the relationships between CRP and the presence of depressive

symptoms or of a clinically relevant major depression (MD)¹² (Table I). Moreover, as it is widely accepted that depression may be a risk factor for the CHD and is often associated with an increased activation of the inflammatory system^{13 14}, these findings have encouraged some researchers to focus their attention on the possible interrelationships between CRP and mood disorders. Moreover, the availability of highly sensitive assays for detecting minor elevations in CRP has improved the ability to detect relationships between inflammation and subsequent diseases¹⁵. The common baseline hypothesis is that depression itself or its related psychological stress may promote inflammatory response by inducing a systemic immune response¹⁶. Some pro-inflammatory cytokine like Interleukin (IL)-6 released in this situation stimulate liver production of acute-phase proteins such as CRP¹⁷. A persistent low grade inflammation should mediate the negative prognostic role played by depression in patients with heart diseases¹⁸. Even if, as above suggested, several studies have examined the relationship between depressive symptoms and CRP, the majority of studies in literature have been limited by retrospective, case-controlled study design, and very few researches have examined the relationship between depression and CRP in a healthy, non-elderly population^{12 19}.

In a small case-controlled study, Sluzewska et al.²⁰ showed that CRP levels were significantly higher in patients with major depression compared with normal controls. One year later Berk et al.²¹ evaluated the level of IL-6 and CRP in 66 depressed patients and 50 controls. Analysis of CRP levels demonstrated raised levels in depressed group patients and the high levels of CRP correlated with raised levels of IL-6. In another study, Rothermundt et al.²² compared serum levels of CRP, a2 macroglobulin, haptoglobin and Interleukin-1 beta between depressed subjects and healthy controls, dividing the depressed group in two subgroups with or without melancholic depression. The two subgroups of patients showed different immune patterns suggesting possible different biological mechanisms involved in the two sub-syndromes. On the other and Kop et al.²³ screened 4268 elderly subjects for depression and CRP levels and found a significantly positive difference between depressed and non-depressed subjects; however, the difference disappeared after adjusting for physical weakness indicators (grip strength,

TABLE I.

Relevant studies on CRP levels and its relationships with depression. *Studi pertinenti sui livelli della proteina C reattiva e i suoi rapporti con la depressione.*

Authors	Study design	Number of subjects	CRP levels
Sluzewska et al. 1996	Case control	49 patients with MD; 15 control subjects	↑ in MD patients
Berk et al. 1997	Case control	66 patients with MD; 50 control subjects	↑ in MD patients
Rothermundt et al. 2001	Case control	43 patients with MD; 43 control subjects	↑ in MD patients with melancholic features
Miller et al. 2002	Case control	50 patients with MD; 50 control subjects	Not increased in depressed subjects when controlling for BMI
Kop et al. 2002	Cross sectional	Community sample of 4268 elderly subjects	↑ in MD patients without physical weakness
Tiemeier et al. 2003	Cross Sectional	Community sample of 3884 elderly subjects	Not increased in depressed subjects
Penninx et al. 2003	Cross sectional	Community sample of 3024 elderly subjects	↑ in MD patients without physical weakness
Stephoe et al. 2003	Cross sectional	Community sample of 226 middle-aged men and women	Not increased in depressed subjects
Ladwig et al. 2003	Cross sectional	Community sample of 3205 middle aged healthy men	↑ in the obese sample with highest level of depression
Danner et al. 2003	Cross sectional	Community sample of 6149 men and women	↑ in males reporting a history of depressive episodes
Douglas et al. 2004	Cross sectional	696 active duty US Army personnel	Weak increase in depressed subjects when controlling for BMI
Ford & Erlinger 2004	Cross sectional	Community sample of 6914 men and women	↑ in males reporting a history of depressive episodes
Schins et al. 2005	Case control	57 depressed post-myocardial infarction patients; 46 non-depressed post- myocardial infarction patients	↑ in MD patients not taking statins ↑ in both groups vs. healthy controls
Empana et al. 2005	Nested case-referent	335 study participants who subsequently developed a first ischemic coronary event; 670 matched controls (2 controls per case)	↑ in subjects with depressive symptoms
Gambi et al. 2005	Retrospective study	37 patients with MD	↑ in MD patients
Elovainio et al. 2006	Cross sectional	Community sample of 1201 young adults	↑ in MD patients
Liukkonen et al. 2006	Cross sectional	Community sample of 1201 young adults	↑ in male MD patients
Kling et al. 2007	Case control	18 unmedicated, remitted women with MD; 18 BMI-matched healthy control subjects	↑ in women with MD

(continues)

TABLE I (follows).

Relevant studies on CRP levels and its relationships with depression. *Studi pertinenti sui livelli della proteina C reattiva e i suoi rapporti con la depressione.*

Authors	Study design	Number of subjects	CRP levels
Bremmer et al. 2007	Cross sectional	Community sample of 1285 elderly subjects	Not increased in depressed subjects
Whooley et al. 2007	Cross sectional	217 outpatients with established CHD and current MD; 767 patients with CHD without MD	↓ in MD patients
Pan et al. 2008	Case control	Community sample of 3289 middle-aged men and women	Not increased in depressed subjects
Henningson et al. 2008	Cross sectional	Community sample of 270 42-year-old women	↑ in women with MD
De Berardis et al. 2009	Cross sectional	145 drug-naïve adult outpatients with MD	↑ in MD patients with higher levels in alexithymic subjects

15-foot walk time, and activity level). Also, Timeier et al.²⁴, in a case-controlled study on 263 elderly subjects with depressive symptoms, found a positive correlation between depression and CRP levels but, as in the above-mentioned study by Kop et al.²³, this relationship disappeared after adjustment for potential confounders (smoking, stroke, functional disability and cognitive score).

Some very interesting studies were published during 2003 and 2004. In the first, Penninx et al.²⁵ examined the link between inflammatory markers and depressed mood in a community-based sample of 3024 well-functioning older people. The Center for Epidemiologic Studies Depression scale (CES-D), a self-report scale to assess depressive symptoms, was employed to identify depressed mood with a cut-off of 16 or higher. The results showed that, compared with the 2879 non-depressed subjects, 145 persons with depressed mood had higher median plasma levels of CRP (1.96 vs. 1.66 mg/l, $p = 0.03$). After dichotomizing the scores of their depression scale and stratifying the CRP levels into quartiles, they demonstrated a correlation between the depressed group and the CRP measurements. After controlling for potential confounders, including body fat mass, this relationship persisted, but only for the highest quartile of CRP levels, not for the first three. Steptoe et al.²⁶ conducted a similarly designed cross-sectional analysis examining the relationship between depression scale scores and CRP in a non clinical middle-aged population in Great Britain. Even without controlling for con-

founders, the researchers found no relationship between depressive symptoms and CRP levels. In a similar study, Schins et al.²⁷ investigated whether depression in 57 post-myocardial infarction patients would be associated with increased CRP levels as compared to 46 non depressed post-myocardial infarction patients. They did not find difference between the two groups, but both of them had CRP levels higher than healthy controls. However, although the difference was not significant when comparing depressed versus non-depressed, the difference became significant when only depressed patients not taking statins were included in the analysis. In 2005, Empana et al.²⁸ conducted a nested case-referent study within the Prospective Epidemiological Study of Myocardial Infarction (PRIME) study of healthy middle-aged men from Belfast and France, and evaluated the baseline CRP from 335 future cases (angina pectoris, non-fatal myocardial infarction, coronary death) and 670 matched controls (2 controls per case). They reported that men with depressive mood had CRP levels 46 percent higher than those without depressive symptoms. These results support the notion of an association of depressive mood with inflammatory markers and suggest that depressive mood is related to CHD even after adjustment for these inflammatory markers. In 2005, our research group²⁹ retrospectively evaluated CRP, total cholesterol and high density lipoprotein levels in 37 adult outpatients with major depression and increased suicide risk. No correlation was found be-

tween total cholesterol and other variables including CRP, but CRP levels resulted a positive predictor of more severe depression and increased suicide risk. The finding of higher levels of depressive symptoms associated with higher levels of CRP, was also confirmed in two studies both conducted on community samples in Finland^{30,31}. Moreover, Kling et al.³² found elevated higher serum levels of CRP in unmedicated, remitted women with MD than body mass index (BMI)-matched healthy control subjects. On the other hand, another study³³ conducted on 3289 chinese subjects aged 50-70, reported no association between depressive symptoms, CRP, other inflammatory markers and adiposity: these findings were also confirmed in another large study conducted on 1285 participants of the Longitudinal Aging Study Amsterdam, aged 65 and over³⁴. In addition, Whooley et al.³⁵ found that depression was associated with even lower levels of CRP in patients with established CHD and current MD.

Recently, in a well conducted and interesting study, Steward et al.³⁶ evaluated the hypothesis that hostility may act together with depressive symptoms to increase serum levels of inflammatory markers relevant to coronary artery diseases. They analyzed serum concentrations of CRP and IL-6 of 316 healthy older adults who completed the Beck Depression Inventory-II and the Cook-Medley Hostility Scale. After adjusting for possible confounding factors, hostility was positively related to serum Interleukin-6 and CRP only among individuals with higher depressive symptoms. These findings suggested that hostility may play a role in increasing inflammatory process relevant to coronary artery diseases only in presence of depressive symptoms. In 2009, De Berardis et al.³⁷ evaluated the relationships between alexithymia, suicide risk, CRP and serum lipid levels in 145 drug-naïve adult outpatients suffering from moderate to severe MD and found that alexithymics showed altered serum lipid levels and higher CRP than non-alexithymics. However, in a linear regression analysis, CRP was not associated neither with depression severity or increased suicide risk.

Relationships between body mass index and C-reactive protein in depression

In a couple of studies, a strong positive correlation has been found between CRP serum levels and BMI³⁸⁻⁴⁰. This may reflect, in part, the fact that adipo-

cytes are the source of a substantial portion of baseline IL-6 production⁴¹ and perhaps also synthesize and secrete some of the baseline CRP itself. Therefore, it was not surprisingly that several studies have suggested that the relationships between CRP and depression may be mediated by adiposity and BMI. Miller et al.⁴², in a case-controlled study, found a persistently significant correlation between CRP, Interleukin-6 and depression than control subjects. But, when correlations between depression and inflammation were adjusted for BMI, group differences for CRP and interleukin-6 were attenuated. These findings suggested that depression' relation with inflammation markers emerges more prominently in subjects with high adiposity and that adiposity would be partially, although not completely, responsible for the elevated levels of inflammatory markers. Similar findings were also found by Ladwig et al.⁴³. They stratified a sample of 3204 subjects (with an age range of 45-74 years) in three levels of depressive mood and found a significant association between increased CRP in the obese sample with highest level of depression in comparison to the obese subjects with a mild or absent depression. These results supported the theory of a possible synergistic effect of obesity and depressive mood on chronic low level inflammation.

One of the most interesting studies on this topic was conducted by Douglas et al.⁴⁴ in 2004. They conducted a cross-sectional study on a cohort of 696 consenting, active duty US Army personnel undergoing a periodic physical evaluation. They studied CRP and measured depressive symptoms using the Patient Health Questionnaire and the depression module of the self-administered version of the Primary Care Evaluation of Mental Disorders (PRIME-MD). The results showed that total depression scores were weakly correlated with CRP and that any correlation between depression scores and CRP was explained by a relationship with BMI. Moreover, this study has some strengths that are, in authors' and our opinion, important: 1) a prospective method of data collection, which is less vulnerable to bias than retrospective cohort data collection; 2) the systematic and precise measurement of variables while blinded to the status of other key variables; 3) the use of validated depression measurement scales with demonstrated internal validity within the population in which it was used and 4) the large size of the study which

permitted the power to rigorously control for potential confounding.

In order to propose a comprehensive model, Miller et al.⁴⁵ examined the inter-relationships between depression, adiposity, and inflammatory molecules implicated in the pathogenesis of coronary heart disease. Using a structural equation modeling (SEM), the authors examined the validity of the several competing models in 100 healthy young adults. The results indicated that a joint pathway model provided the best description of the inter-relationships between depression, adiposity, and inflammation in healthy young adults: the model was consistent with the hypothesis that depressive symptoms may promote weight gain, which in turn activates an inflammatory response through at least two distinct pathways. The first pathway may involve the expanded adipose tissue synthesizing and releasing IL-6 at elevated concentrations that may influence the liver, where it induces expression of CRP. The second pathway involves expanded adipose tissue releasing higher leptin concentrations that may upregulate the expression of IL-6, which in turn may enhance hepatic release of CRP.

Gender differences in C-reactive protein levels in depression

Several studies have suggested that gender differences in CRP levels may exist in depressed subjects. Danner et al.⁴⁶ demonstrated an association between depression and serum CRP levels in men. Researchers analyzed data from the Third National Health and Nutrition Examination Survey (NHANES III), a representative sample of the US population from 1988 to 1994, wherein the participants included a total of 6,149 individuals aged 17 to 39 years who were free from cardiovascular diseases and chronic inflammatory conditions. In particular, the results pointed out that, compared with men without a history of depression, men reporting a history of depressive episodes had significantly higher odds of having elevated CRP levels than men without history of depressive symptoms after adjustment for a number of potential confounding factors. Furthermore, in contrast to the results for men, they failed to find that depression was significantly related to CRP levels in women. Another well designed and conducted study analyzed data from the Third National Health and Nutrition Examination Survey⁴⁷ and found an

association between history of MD and elevated CRP levels that was present even after accounting for multiple potential confounders, but there was no indication of any association between CRP level and depression in women, despite a higher prevalence of depression and elevated CRP level in women than in men. These results were also confirmed in a Finnish study conducted on a large samples of subjects³¹ that showed that, in males but not in females, elevated CRP levels increased the probability for severe current and recurrent depressive episodes.

A recent study by Henningson et al.⁴⁸ tested the association between CRP serum levels and personality traits in 270 42-years-old women and gave different results. For the assessment of personality, the Temperament and Character Inventory (TCI) was used. They found that the temperament trait harm avoidance was positively, and the character trait self-directedness negatively, associated with CRP levels in a population-based cohort of women. Furthermore, women who reported an ongoing depression showed significant higher levels of CRP than women denying being depressed. This means that CRP may be considered as state marker of depression at least in a sample of women with clinically relevant depressive symptoms.

Effect of antidepressant treatment on C-reactive protein levels in depression

There are five studies that evaluated CRP levels during treatment of MD (Table II). Lanquillon et al.⁴⁹ assessed 24 inpatients with MD both before and during 6 weeks of antidepressant (amitriptyline) treatment. They found that the levels of CRP were significantly increased at admission and decreased in both responder and non-responder patients during antidepressant treatment. Tuglu et al.⁵⁰ measured tumor necrosis factor (TNF)-alpha, CRP serum concentrations, erythrocyte sedimentation rate and leukocyte count in 26 MD patients and in 17 control subjects. The measurements were repeated after six weeks of antidepressant treatment with selective serotonin reuptake inhibitors. The comparison of pre- and post-treatment measurements revealed that CRP together with TNF-alpha and leukocyte count decreased to levels comparable with those of the control subjects and may be considered as potential state markers in MD. On the other hand, Corcoran et al.⁵¹ studied CRP and pro- and anti-inflammatory cy-

TABLE II.

Studies that evaluated CRP levels after treatment of major depression. *Studi che hanno valutato i livelli di proteina C reattiva dopo trattamento della depressione maggiore.*

Authors	Treatment	Number of patients	Duration of follow-up	Effect on CRP levels at endpoint
Lanquillon et al. 2000	Amitriptyline	24	6 weeks	↓ after treatment
Tuglu et al. 2003	SSRIs	26 patients and 17 controls		↓ after treatment
Corcoran et al. 2005	Vagus nerve stimulator	10 patients with resistant MD	3 months	No change
Piletz et al. 2008	Venlafaxine	12	8 weeks	No change
Tousoulis et al. 2009	Several TCAs, SSRIs and SNRIs	145 adult outpatients with heart failure and MD	6 months	↓ in patients treated with TCAs/SNRIs

tokines in a sample of 10 patients with resistant depression in the weeks prior to, and 3 months following, implantation of a Vagus nerve stimulator. They observed that plasma CRP levels remained unchanged after the Vagus nerve stimulation. Moreover, it has been demonstrated that levels of CRP in depressed patients did not change after 8 weeks of venlafaxine treatment⁵². Recently, Tousoulis et al.⁵³ evaluated 250 patients with heart failure (154 suffering from MD). Patients with MD were under selective serotonin reuptake inhibitors (n = 120) or tricyclic antidepressants (TCA) and/or serotonin/norepinephrine reuptake inhibitors (SNRIs) (n = 34), for at least 6 months. They found that

CRP levels were significantly lower in patients receiving TCAs/SNRIs compared to patients receiving SSRIs or those without depression.

C-reactive protein and bipolar disorders

Bipolar disorder (BD) is characterised by the occurrence of one or more manic episodes or mixed episodes, often accompanied by one or more major depressive episodes. Concerning BD, despite its severity and prevalence, there is a relative lack of studies investigating CRP levels (Table III).

Hornig et al.⁵⁴ retrospectively evaluated CRP lev-

TABLE III.

Relevant studies on CRP levels in bipolar disorder. *Studi pertinenti sui livelli della proteina C reattiva nel disturbo bipolare.*

Authors	Study design	Number of patients	CRP levels
Retrospective study	79 patients study	79 patients with BD-I; 24 patients with BD-II; 46 with MD; 22 control subjects	↓ in BD patients treated with lithium
Wadee et al. 2002	Case control	45 patients with BD (manic episode); 45 control subjects	No differences than control subjects
Huang and Lin 2007	Case control	23 patients with MD, 13 with BD (manic episode) and 31 healthy controls	↑ in BD patients during manic episode
Dickerson et al. 2007	Cross sectional	122	↑ in patients with manic symptoms
De Berardis et al. 2008	Retrospective study	90	↑ both in manic and depressive episodes

els in 79 bipolar I, 24 bipolar II and 46 unipolar depressed outpatients in comparison to 22 healthy controls. The results showed that patients on lithium monotherapy were significantly less likely to demonstrate elevated CRP, and a similar trend was noted in those patients taking lithium in combination with an antidepressant. The frequency of elevated CRP levels did not significantly vary for different psychotropic medications, affective subgroups, or mood states. Wade et al.⁵⁵ evaluated CRP in the sera of 45 patients each suffering from an acute manic episode compared with 45 controls and found that, although the mean CRP level was raised in the patients' group, it did not reach statistical differences from the controls. In 2007, Huang and Lin⁵⁶ analyzed the CRP serum level in 23 patients affected from depressive disorder, 13 affected from bipolar disorder I (manic episode) and 31 healthy controls. The two patients groups had higher mean serum CRP levels than the controls, but using analysis of covariance with age adjustment, only the values of the bipolar group reached statistical significance. This results suggest that patients with bipolar I disorder might have a more severe inflammation than patients with major depression, but this could be due to many external factors, such as life-style, hyperactivity or drug abuse. On the other hand, Dickerson et al.⁵⁷ found that elevated serum levels of CRP were associated with mania symptoms in outpatients with bipolar disorder with CRP levels significantly associated with the Young Mania Rating Scale scores.

Recently, our research group conducted a retrospective study analyzing medical charts of 90 adult outpatients with BD to evaluate serum CRP levels and total cholesterol (TC)⁵⁸. We found an overall elevation of CRP levels during manic and depressive episodes of BD along with a significant decrease in TC levels during the same episodes. Considerably, we found differences in CRP and TC levels based on the current mood state. This would suggest that the both CRP and TC levels in BD may be influenced by the acute mood state. Why cholesterol levels would be low and CRP higher in the manic and depressive episodes is unclear, necessitating further prospective studies.

C-reactive protein and schizophrenia

Schizophrenia is a major mental illness characterised by hallucinations, delusions, apathy and social withdrawal, and cognitive impairment, which results in impaired functioning in work, school, parenting, self-care, independent living, interpersonal relationships, and leisure time⁵⁹⁻⁶⁰. Among psychiatric disorders, schizophrenia is the most disabling and requires a disproportionate share of mental health services⁶¹.

Even if the involvement of immune dysfunction and inflammation have been widely described in patients with schizophrenia⁶²⁻⁶⁴, in contrast, few studies examined the role of CRP in schizophrenia (Table IV). Shcherbakova et al.⁶⁵ pointed out that the acute stage of Schizophrenia was accompanied

TABLE IV.

Relevant studies on CRP levels in schizophrenia. *Studi pertinenti sui livelli della proteina C reattiva nella schizofrenia.*

Authors	Study design	Number of patients	CRP levels
Shcherbakova et al. 1999	Cross sectional	30	↑
Mazzarello et al. 2004	Case control	24	↑
Fan et al. 2007	Cross sectional	26	↑ in a subgroup of patients with more severe negative symptoms
Dickerson et al. 2007	Cross sectional	413	↑ in patients with impaired cognitive functioning
Baptista et al. 2007	Longitudinal study	60 patients treated with typical antipsychotics and switched to olanzapine	↑ in patients after switch to olanzapine
Carrizo et al. 2008	Retrospective study	88 patients; 34 first degree relatives	↑ in patients treated with typical antipsychotics

by increased level of CRP and by the activation of plasma kallikrein-kinin system on the background of enhance in the functional activity of the alpha-1-proteinase inhibitor. This observation was confirmed by Mazzarello et al.⁶⁶ who found increased serum CRP concentration in 24 patients affected by Schizophrenia.

In the 2007, Fan et al.⁶⁷ have examined the hypothesis that elevated serum levels of CRP might be associated with more severe clinical symptoms in 26 patients with schizophrenia. The elevated CRP group (5 subjects with CRP levels > 0.5 mg/dl) had significantly higher Positive and Negative Syndrome Scale (PANSS) total score, PANSS negative symptoms subscale score and general psychopathology subscale score compared with the normal CRP group (21 subjects with CRP levels ≤ 0.50 mg/dl). The groups did not differ on the PANSS positive symptoms subscale score. These differences in PANSS scores were not explained by other variables as researchers found that there were no significant differences between the normal/elevated CRP groups regarding demographic and general clinical characteristics, such as age, gender, race, education level, age of illness onset, history of substance use, smoking status, WBC and current antipsychotic medication used. On the other hand, Dickerson et al.⁶⁸ conducted an interesting study on a large sample (413 schizophrenic patients). They analyzed CRP serum level and PANSS scores. Moreover, they administered a brief cognitive test battery, the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) based on 5 scales: Immediate Memory, Visuo-Constructional, Language, Attention, and Delayed Memory. They found that 127 subjects (26.1%) had a CRP level ≥ 5.0 mg/μl (elevated level group) whereas 286 subjects had a CRP level < 5.0 mg/μl (normal level group). The two CRP group did not differ for the positive, negative or general PANSS scores. However, the subjects with higher CRP levels reported significantly lower mean RBANS scores. Therefore, authors concluded that CRP level and cognitive functioning may be related in individuals with schizophrenia, independently of psychopathology. In fact, it may be that cognitive measures are more stable in patients with schizophrenia than are symptom measures, and thus more sensitive to the effects of CRP, but further prospective studies are needed in order to clarify this topic.

Recently, Carrizo et al.⁶⁹ evaluated several blood factors associated with coagulation (fibrinogen, plasminogen activator inhibitor and antithrombin III) and inflammation-related factors (CRP and leptin) in schizophrenic patients chronically treated with typical and atypical (clozapine and olanzapine) antipsychotics and their first-degree relatives. They found that patients treated with typical antipsychotics showed the highest CRP level in spite of having the lowest BMI. Moreover, schizophrenic patients as a single group had higher CRP levels than relatives. Authors argued that elevated CRP levels associated to antipsychotic treatment might be an additional factor in the metabolic dysfunction often observed in schizophrenia; interestingly, they further suggested that the observed high CRP levels in the patients treated with typical antipsychotics in spite of their low BMI may be related to the low socioeconomic status of these subjects which may promote subclinical inflammation related to smoking, substance abuse, poor dietary and hygiene habits. These results are in line with those of a previous study that showed an increase in CRP levels after 8 weeks of treatment with olanzapine among sixty patients (26 women and 34 men) with severe schizophrenia undergoing chronic hospitalization and whose conventional antipsychotic treatment were switched to olanzapine⁷⁰.

Conclusions

The data available about the role of CRP as a low grade inflammation marker in psychiatric disorders are still contradictory. Even if some studies have pointed out a relationships between severity of some psychiatric disorders such as depression, bipolar disorder and schizophrenia and elevated CRP levels, it is possible that these relationships may be mediated by BMI and/or gender effects. Therefore, in order to consider CRP as a state marker of certain psychiatric disorders, the influence of potential confounding factor should be excluded. Anyway, to date, the relative lacking of prospective studies on this topic, does not to allow definitive conclusions and further studies are needed.

Concerning limitations of the present paper, it should be considered that this was a narrative review. This type of review is useful where the aggregation of data is difficult because diverse studies or fields are being analysed, but the methodology is

less strict than that of a systematic review. Furthermore, reviews that do not use methodologically solid methods employed in systematic reviews are very susceptible to bias and confounding and serve mainly to discuss an issue rather than present an accurate summary of the literature. However the present paper is, to date, the only that reviewed relationships between CRP and psychiatric disorders and may be useful as a basis for future systematic reviews.

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