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Abnormal C-reactive protein blood levels as a specific biomarker of major depression and non-remission under antidepressants in schizophrenia

Guillaume Fond, J.A. Micoulaud-Franchi, M. Faugere, L. Boyer, C. Faget-Agius, C. Lançon, R. Richieri, M. Cermolacce

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1 Abnormal C-reactive protein blood levels as a specific biomarker of major depression and non-
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4 Fond G ^{1,2*}, Micoulaud-Franchi JA, Faugere M ^{1,2}, Boyer L ^{1,2}, Faget-Agius C ^{1,2}, Lançon C ^{1,2},
5 Richieri R ^{1,2,6}, Cermolacce M ^{1,2},

6 1Department of Psychiatry, La Conception University Hospital, 13005 Marseille, France.

7 2 EA 3279 – EA 3279: CEReSS - Health Service Research and Quality of Life Center, 27 Boulevard
8 Jean Moulin, 13005 Marseille, France

9 3 SHU Adult Psychiatry, Sainte Marguerite University Hospital, 13274 Marseille, France.

10

11

12 *** Correspondence should be sent to: Dr Guillaume FOND**

13 AP-HM, Aix-Marseille Univ, Faculté de Médecine - Secteur Timone, EA 3279: CEReSS -Centre
14 d'Etude et de Recherche sur les Services de Santé et la Qualité de vie, 27 Boulevard Jean Moulin,
15 13005 Marseille, France

16 Tel: (33 6 68 10 22 58), e-mail: guillaume.fond@ap-hm.fr

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1 **Abstract**

2 **Background.** C-reactive protein (CRP) is a general marker of peripheral inflammation and has been
3 shown to be a good marker of neuroinflammation. CRP has been found to be elevated in patients with
4 mood disorders (especially unipolar disorders (UD) and in schizophrenia (SZ)) but also to be lowered
5 by antidepressants.

6 **Objective:** The objectives were (i) to determine the prevalence of major depression, antidepressant
7 prescription and remission under antidepressant in a stabilized population of SZ and UD patients
8 consulting in a daily hospital, and (ii) to determine if CRP was a marker of major depression and
9 remission under antidepressant in these SZ and UD populations.

10 **Methods:** Abnormal CRP was defined by a CRP blood level $\geq 3\text{mg/L}$. Depressive symptoms were
11 assessed by the Calgary Depression Rating Scale score. The clinicians were blinded of the CRP status
12 of the patient.

13 **Results:** 411 patients were included (272 SZ and 139 UD). 171 (41.6%) were diagnosed with current
14 major depression (74 (27.2%) for SZ and 97 (69.8%) for UD). 86 SZ (31.6%) and 119 UD (85.6%)
15 were treated by antidepressant. Only 28/74 (37.8%) of the SZ subjects with major depression were
16 administered antidepressants vs. 87/97 (89.7%) for UD. The non-remission rate under antidepressant
17 was 28/86(32.6%) for SZ and 87/119 (73.1%) for UD. Overall, 105 (40.1%) of SZ and 39 (28.1%) of
18 UD patients were found to have abnormal CRP blood levels. Abnormal CRP levels were significantly
19 associated with increased MDD and **more strongly with** increased rates of non-remission under
20 antidepressants in SZ patients, independently of age, gender, psychotic symptomatology, functioning,
21 tobacco smoking and metabolic syndrome. This result was not replicated in UD patients, which
22 suggests that CRP may be a specific marker of major depression and remission under antidepressant in
23 SZ patients.

24 **Conclusion:** The development of biomarkers in psychiatry may orientate specific etiologic therapies in
25 patients with mental disorders. The present findings suggest that major depression is frequent in SZ
26 patients and that increased CRP levels are associated with non-remission under antidepressants in this
27 population. **Anti-inflammatory** strategies may be particularly useful in this specific population.

28

29 **Keywords:** inflammation; schizophrenia; major depression; antidepressant; biomarker

30

1 **1. Introduction**

2 Major depression is frequent across severe mental disorders (including schizophrenia (SZ) and
3 unipolar disorders (UD)) and responsible for a high part of poor prognosis, impaired functioning and
4 quality of life in these patients (Guillaume Fond et al., 2018a). In schizophrenia, almost half of the
5 patients have a major depression issue. Among them, one third is correctly diagnosed and treated with
6 antidepressants, one third is diagnosed and treated but unremitted, and one third is non-diagnosed and
7 non-treated (Guillaume Fond et al., 2018a). One explanation may be the difficulty to detect major
8 depression in SZ patients that exhibit more frequently hostility, impaired help seeking and blunted
9 affect. Developing a biomarker of major depression in schizophrenia would therefore be useful to
10 improve its detection and treatment. In the same line, identifying a predictor of antidepressant
11 remission may help clinician to guide personalized interventions in SZ patients with major depression.

12 Immunopsychiatry has yielded major findings in the last two decades. Among those, each severe
13 mental disorders has been associated with specific immune-inflammatory disturbances (Guillaume
14 Fond et al., 2015). Blood highly-sensitive C-reactive protein (hs-CRP) is the most common biomarker
15 of chronic peripheral inflammation and has been recently shown to be also a good biomarker of
16 central/brain inflammation (Felger et al., 2018). C-reactive protein is produced by the liver in response
17 to the increase of the interleukin-6, an interleukin that has been found to be increased in both SZ and
18 UD (Guillaume Fond et al., 2015).

19 In a recent systematic review, we have concluded that increased CRP may be considered as a
20 biomarker for SZ onset risk, as well as a risk factor for increased positive symptoms, cognitive
21 impairment in SZ subjects (Guillaume Fond et al., 2018b). CRP has been recently shown to be a
22 biomarker of resistance into antipsychotic treatment in SZ subjects (G. Fond et al., 2018a). CRP may
23 also be particularly increased in patients with metabolic syndrome or tobacco smoking, two major
24 sources of inflammation in SZ subjects (Fond et al., 2017a).

25 Beyond SZ, increased CRP has been extensively associated with depressive symptoms in general
26 population and mood disorders, and antidepressants have been found to have anti-inflammatory effects
27 (Hannestad et al., 2011). On the contrary, conflicting results were found for the association between
28 CRP and depressive symptoms as well as on the effect of antidepressants in SZ patients (Faugere et
29 al., 2018; Fond et al., 2016). Given that SZ and UD have been associated with different
30 immunological disturbances, these different immune-inflammatory signatures may explain these
31 discrepancies. However, SZ and UD depressive symptoms as well as the response to antidepressants
32 have never been directly compared to determine if CRP was a biomarker of major depression in both
33 SZ and UD patients. Moreover, no study has explored the association between increased CRP and
34 remission under antidepressants. If antidepressants have anti-inflammatory effects, one may
35 hypothesize that increased CRP may be associated with non-remission under antidepressants.

1 The objective of the present study was to determine if abnormal hs-CRP blood levels were a
2 biomarker of increased major depression and increased non-remission under antidepressant in
3 respectively SZ and UD patients.

4 5 **2. Methods**

6 **2.1 Study participants**

7 The patients were consecutively recruited in the daily psychiatric academic hospital from Sainte-
8 Marguerite hospital, Marseille, France, from October 2010 to May 2015. The inclusion criteria were:
9 (1) age 18-85 years old, (2) diagnosis of SZ or UD according to the DSM-IV-TR criteria, (3) French as
10 native language (4) stabilized with a background treatment (antipsychotic and/or antidepressant) for at
11 least 8 weeks. The exclusion criteria were: (1) chronic somatic illness and specifically inflammatory or
12 central nervous system illness and (2) mental retardation.

13 **2.2 Ethical statement**

14 The data collection was approved by the Commission Nationale de l'Informatique et des Libertés
15 (CNIL number 1223715). The study was designed in accordance with the Declaration of Helsinki and
16 French good clinical practice. All of the patients were informed of the study and gave written informed
17 consent.

18 **2.3 Data Collection.**

19 The following data were collected:

20 Chronic peripheral inflammation

21 Serum highly-sensitive CRP (hs-CRP) levels were determined using sensitive regular immunoassays
22 (ELISA). The results were expressed as milligram per liter. The detection limit was 0.08 µg/ml.
23 Patients were classified into two groups: normal CRP level (≤ 3.0 mg/l) and high CRP (> 3.0
24 mg/l)(Wysokiński et al., 2014).

25 Major depression

26 Major depression was evaluated with the Calgary Depression Rating Scale (CDSS) (Addington et al.,
27 1993) that was validated from a long time in SZ but only recently in UD (Micoulaud-Franchi et al.,
28 2018). The Major depression group was defined by a CDSS score ≥ 6 .

29 Remission was defined by a CDSS score < 6 under antidepressant (Guillaume Fond et al., 2018a). The
30 unremitted group was defined by a CDSS score ≥ 6 under antidepressant.

31 Other variables

1 Socio-demographic information (gender, age) was reported. SZ symptomatology was assessed using
2 the Positive And Negative Syndrome Scale (PANSS) (Kay et al., 1987). Daily global functioning was
3 evaluated with the Global Assessment of Functioning Scale (GAF) (Startup et al., 2002). Alcohol
4 consumption was assessed by the Alcohol Use Disorders Identification Test (AUDIT) (Saunders et al.,
5 1993). Illness duration; tobacco consumption, drug information: antipsychotic and antidepressant
6 treatment were also reported.

7 Metabolic Syndrome definition (Grundy, 2005): Sitting blood pressure (BP) and anthropometrical
8 measurements were recorded. Two BP measurements were made 30 seconds apart in the right arm
9 after the participant had sat and rested for at least 5 minutes. A third BP measurement was made only
10 when the first two BP readings differed by more than 10 mm Hg. The average of the 2 closest readings
11 was used in the analysis. Waist circumference was measured midway between the lowest rib and the
12 iliac crest with the subjects standing. This was performed with a tape equipped with a spring-loaded
13 mechanism to standardize tape tension during measurement. Body mass index (BMI) was calculated
14 as weight in kilograms divided by the square of the height in meters. Overnight fasting blood was
15 collected for metabolic profiles analysis. Fasting levels of serum triglyceride (TG) and fasting plasma
16 glucose were measured by an automated system, and serum high-density lipoprotein cholesterol
17 (HDL-C) level was measured by electrophoresis. Metabolic syndrome was defined according to the
18 modified criteria of the International Diabetes Federation (IDF) (Alberti et al., 2006), which requires
19 the presence of three or more of the following five criteria: high waist circumference (>94 cm for men
20 and >80 cm for women), hypertriglyceridemia (≥ 1.7 mM or on lipid lowering medication), low HDL
21 cholesterol level (<1.03 mM in men and < 1.29 mM in women), high blood pressure ($\geq 130/85$ mmHg
22 or on antihypertensive medication), high fasting glucose concentration (≥ 5.6 mM or on glucose-
23 lowering medication).

24 Double-blinded assessment: Depression assessment and antidepressant reporting were blinded of the
25 CRP status and blood CRP dosage was blinded of the clinical evaluation.

26

27 **2.4 Statistical analysis**

28 Socio-demographics, clinical characteristics, addictive behavior and treatments are presented using
29 measures of means and dispersion (standard deviation) for continuous data and frequency distribution
30 for categorical variables. The data was examined for normal distribution with the Shapiro-Wilk test
31 and for homogeneity of variance with the Levene test. Comparisons between respectively MDD and
32 non-MDD, and remitted and non-remitted individuals regarding demographic, clinical characteristics
33 were performed using the chi-square test for categorical variables. Continuous variables were analysed
34 with Student t-tests for normally distributed data and in case of normality violation, additional Mann-
35 Whitney tests were performed to confirm the result.

1 Variables with P values < 0.20 in univariate analysis were included in the multivariate logistic
2 regression model of factors associated with respectively MDD (table 1 and 3) and unremitted MDD
3 (table 2). Tobacco smoking and metabolic syndrome were forced due to their relationship with both
4 depression and inflammation (Fond et al., 2017a; Godin et al., 2015, 2017; Rey et al., 2017). Only
5 total PANSS score was included in the multivariate model and not its subscores that are highly
6 correlated. The final models included odds ratios and 95 % confidence intervals. This study was a
7 confirmatory analysis. No correction for multiple testing has therefore been carried out, which is
8 consistent with recommendations (Bender and Lange, 2001). Analyses were conducted using SPSS
9 17.0 software (SPSS Inc., Chicago, IL). All statistical tests were two-tailed, with α level set at 0.05.

11 3. Results

12 Overall, 411 patients were included (272 SZ and 139 UD) (Flow chart figure 1). 171 (41.6%) were
13 diagnosed with current major depression (74 (27.2%) for SZ and 97 (69.8%) for UD). 86 SZ (31.6%)
14 and 119 UD (85.6%) were treated by antidepressant. Only 28/74 (37.8%) of the SZ subjects with
15 major depression were administered antidepressants vs. 87/97 (89.7%) for UD. The non-remission rate
16 under antidepressant was 28/86=32.6% for SZ and 87/119 (73.1%) for UD.

17 Overall, 105 (40.1%) of SZ and 39 (28.1%) of UD patients were found to have abnormal CRP
18 blood levels.

19 Abnormal CRP levels were found to be associated with major depression in SZ subjects
20 independently of age, gender, psychotic symptomatology, functioning, antidepressant treatment,
21 tobacco smoking and metabolic syndrome (aOR= 1.872, p=0.049) (Table 1). Moreover, abnormal
22 CRP levels were also found to be associated with non-remission under antidepressant in SZ subjects
23 independently of age, gender, psychotic symptomatology, functioning, tobacco smoking and metabolic
24 syndrome (aOR=3.328, p=0.034) (Table 2). No association was found between peripheral
25 inflammation and major depression (Table 3) or remission (data not shown) in UD subjects.

27 4. Discussion

28 Altogether, our results may be summarized as follows: in a large sample of stabilized
29 community-dwelling patients with severe mental disorders consulting in a daily hospital, major
30 depression is frequent as well as non-remission under antidepressant. Abnormal CRP levels appear as
31 a biomarker of both major depression and non-remission under antidepressant in schizophrenia but not
32 in unipolar disorders independently of age, gender, tobacco smoking and metabolic syndrome.

1 Abnormal CRP was associated with major depression. This result may yield a major finding to
2 guide the detection and treatment of major depression in SZ subjects. We found that around 40% of
3 SZ subjects were identified with increased CRP levels and that almost a half of those with abnormal
4 CRP were identified with major depression (vs. 36% in those without). These rates are higher than
5 those found in a recent national study carried out in the French Expert Center Network (Fond et al.,
6 2016). This suggests that the rate of both depression and peripheral inflammation may vary across
7 stabilized community-dwelling SZ patients due to multiple environmental factors including
8 psychotropic drugs, diet, physical activity and sleep may influence both depressive symptoms and
9 peripheral inflammation (Fond et al., 2017b; Lassale et al., 2018). This suggests that modifying these
10 variables may decrease major depression as well as inflammation in SZ subjects. It should be
11 underlined that our results were adjusted for smoking and metabolic syndrome, two major sources of
12 inflammation in SZ subjects (Schürhoff et al., 2018).

13 Abnormal CRP levels have also been found to be associated with increased non-remission
14 under antidepressants in schizophrenia with a stronger association than with depression. As mentioned
15 in the rationale of the present study, antidepressants have shown anti-inflammatory properties in non-
16 SZ subjects (Hannestad et al., 2011) but the effect of antidepressants on peripheral inflammation in SZ
17 subjects is unclear (Faugere et al., 2018; Fond et al., 2016). The present results suggest that persistent
18 increased CRP under antidepressant is a biomarker of non-remitted major depression in schizophrenia.
19 This may suggest that anti-inflammatory strategies may be effective in addition or in replacement of
20 antidepressant drugs in SZ subjects. Among those, omega 3 fatty acids and vitamin D appears as the
21 treatments of choice that have shown anti-inflammatory and antidepressive properties in non-SZ
22 populations (Sarris et al., 2016) as well as physical activity that has anti-inflammatory properties
23 (Curcic et al., 2017). Other anti-inflammatory drugs including celecoxib have also shown
24 effectiveness, however with more long-term side effects (Cho et al., 2019; Sommer et al., 2013).
25 Nutritional interventions combined with physical activity appear as promising programs to improve
26 depression and remission in SZ subjects with a good benefit/risk ratio.

27 These results have not been replicated in UD subjects, contrary to what could have been
28 expected from previous studies (Köhler et al., 2017). These negative results may be explained by the
29 effect of antidepressants that have shown anti-inflammatory properties in non-SZ populations (Köhler
30 et al., 2018) but not in SZ populations (Fond et al., 2016). Most of the UD patients were treated by
31 antidepressants, which may explain the lower rates of abnormal CRP in this population. The UD
32 participants were fewer in number than SZ, however the high rates of major depression, antidepressant
33 treatments, non-remission under antidepressant and abnormal CRP levels enable sufficient statistical
34 power to explore the associations between those variables.

1 In our study, the subjects with major depression were more than twice more likely to be
2 administered antidepressants if they were diagnosed with UD than with SZ. This result may be
3 explained by a prescription bias, as antidepressants have been suggested for long to be more effective
4 in non-SZ subjects. However, recent data suggest that antidepressants are effective in both schizophrenic
5 and non-schizophrenic major depression and should be equally prescribed in SZ and UD (Guillaume
6 Fond et al., 2018a). Moreover, treating psychiatrists may be afraid of a worsening of aggressiveness
7 under antidepressants. However, antidepressants have not been associated with increased aggressiveness
8 in SZ patients in previous studies (G. Fond et al., 2015; Fond and Boyer, 2016). The SZ patients with
9 major depression may be underdiagnosed due to confusion between major depression and negative
10 symptoms (including anhedonia, blunted affect and lack of motivation). These results are consistent
11 with those of previous studies (G. Fond et al., 2018b; Guillaume Fond et al., 2018a) and highlight the
12 need to improve the detection of major depression in SZ subjects.

13 Metabolic syndrome has been found to be associated with major depression in schizophrenia
14 independently of inflammation in our results. This result is consistent with previous findings of the
15 FACE-SZ cohort, a national cohort of SZ patients, in which major depression was the best predictor of
16 rapid high weight gain and metabolic syndrome at one year (Godin et al., 2017). Metabolic syndrome
17 and depression may have a bilateral relationship by decreased physical activity and common risk
18 factors like poor diet. Depression has been associated with several components of metabolic syndrome
19 including carbohydrates and lipids disturbances (Suttajit and Pilakanta, 2013; Tharmaraja et al., 2019).

20 Limits. Psychotherapies have not been reported in the present study. However it is unlikely
21 that psychotherapy may influence the association between peripheral inflammation and major
22 depression. Lifestyle variables (diet, physical activity, sleep) and complementary agents intake have
23 not been reported and may have impacted both depression and inflammation.

24 Strengths. The present study is the first study comparing the relationship between abnormal
25 CRP and major depression in two severe mental disorders. The highly-sensitive CRP was used to
26 detect low-grade peripheral inflammation (Bulzacka et al., 2016). Major depression has been evaluated
27 for the first time with the same validated scale in the two disorders.

28 Conclusion

29 Major depression is frequent in both stabilized subjects with SZ and UD consulting in a daily
30 hospital. UD subjects were more than twice more likely than SZ to receive antidepressants in case of
31 major depression while antidepressants may be effective in both populations. Abnormal CRP is a
32 proxy for peripheral inflammation and was found in the present study to be a biomarker of major
33 depression and non-remission under antidepressants in schizophrenia. Hs-CRP dosage may therefore
34 improve major depression diagnosis in SZ subjects and guide clinicians toward anti-inflammatory
35 strategies to improve remission in this specific population.

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Conflicts of interest: no conflicts to disclose.

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