C-Reactive Protein and Aggression in Patients with Schizophrenia

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Abstract: Recent studies reported firstly an association between aggression and inflammation and secondly an association between inflammation and schizophrenia. In this study, we aim to explore the association between the clinical signs of schizophrenia, aggressive behavior in patients with relapsing schizophrenia and inflammatory marker: CRP (C-reactive protein). Adult schizophrenia inpatients without affective symptoms (n = 154) were prospectively identified and categorized according to their C-reactive protein measurement at admission as either elevated (CRP > 5 mg/L; n = 52) or normal (CRP < 5 mg/L; n = 102). The following indicators of aggression were compared: PANSS excitement component (PANSS-EC), restraints, injectable treatment 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. Inpatients with elevated C-reactive protein displayed increased aggressive behavior compared to patients with normal CRP levels (<5 mg/L). This was manifested by increased PANSS-EC score (p=0,0001), higher rates of restraint during hospitalization (p=0,0001), higher use of injectable treatment (0,0001) and existence of suicidal behavior (p=0,001). Multivariate analysis revealed that Lymphocyte count, total PANSS score, PANSS excitement score were independently associated with a CRP> 5 mg/L. These results confirm the role played by inflammation and immunity in the appearance of aggressive behavior in schizophrenic patients and highlight the interest of the CRP assay at the admission of patients as an indicator of aggression in hospitalized schizophrenic patients.

Keywords: Schizophrenia, Inflammation, Aggression, CRP

1. Introduction

Schizophrenia is a psychiatric disorder, of prolonged and disabling evolution. Its prevalence is estimated between 0.4% to 1% and it is a public health problem on a National and International level. In Morocco, the National Survey of Prevalence of Mental Disorders in the general population aged 15 and over revealed that 5.6% suffer from a psychotic disorder and that more than 200.000 Moroccans aged 15 and over, suffer from Schizophrenia [1].

The fact that schizophrenia would be one of the most incriminated psychiatric disorder in the acting out is comforted by several data from the scientific literature, schizophrenic subjects show twice an aggressive behavior compared to the general population according to the report of the HAS on psychiatric dangerousness [2]. The risk of violence would be increased during relapses episodes of manic excitement, hallucinatory episodes or a florid outbreak of symptoms of schizophrenia [3].

Aggressive behavior is one of the leading causes of admission to a psychiatric institution and may endanger the caregiver, the patient, and other patients in the ward, hence

the value of studying the clinical and biological signs that accompanies this behavioral disorder. A study in Germany revealed a prevalence of aggression at 7.7% [4]. Similar studies in Australia and New Zealand have shown a prevalence of aggressive behavior from 11.3% to 15% [5, 6].

CRP is a protein produced by hepatocytes after an acute or chronic inflammatory state. It is a nonspecific marker of inflammation and is associated with several pathologies, including coronary artery disease, stroke and peripheral vascular disease [7]. A meta-analysis revealed a significant increase in CRP levels in patients with schizophrenia compared to a control population [8]. However, few publications have addressed the association between aggressive behavior in patients with relapsing schizophrenia and CRP (C-reactive protein), as a biomarker. In our study, we aim to explore this relationship, the clinical signs of schizophrenia and sociodemographic data of patients; while making the assumption that patients with high CRP blood levels would be the most aggressive.

2. Method

2.1. Type of Study

This was a cross sectional study of 154 patients with schizophrenia according to the diagnostic criteria of the fifth version of DSM [9], divided into two groups according to the CRP level.

2.2. Population Studied and Sampling

All schizophrenic patients who were hospitalized in the Psychiatry Department at the University Hospital in Marrakech from the first of March 2017 to the 31st of May 2017 are recruited after informed voluntary consent.

2.3. Exclusion Criteria

We excluded patients with schizoaffective disorder, depression, bipolar disorder, and patients with organic pathology or fever over 37.9 C and those who were treated with antibiotic, anti-inflammatory and anti-pyretic medications.

2.4. Variables

Data extraction from the charts were based on predesigned form which includes socio demographic measures and clinical features.

Socio demographic factors: Information was obtained from the admission charts for each patient and contains information regarding sex, age, level of education, marital status, and family history.

Clinical, therapeutic and biological features of schizophrenia: Age of onset, duration of disease, use of licit and illicit substances, psychopathological evaluation of schizophrenia was made using the positive and negative syndrome scale (PANSS) [10], PANSS excitement component (PANSS-EC) [11, 12] and PANSS depression

component [13]. Biological items: CRP results, white blood cells, neutrophils, lymphocyte cells.

The evaluation of aggressiveness was made based on four clinical criteria: the PANSS score EXCITEMENT on admission, the use of restraint, the presence of suicidal ideation or suicide attempts and the administration of injectable treatment.

The evaluation of the clinical status of the patient by the PANSS score was determined by the patient's treating psychiatrist following an interview that was conducted within 48 hours from admission as a routine practice of the inpatient unit.

2.5. Laboratory Procedures

Blood sampling and determination of CRP: The blood sample was taken from each patient admitted systematically within a 24 hours maximum delay after admission, in the morrning after fasting for 10 h. CRP is part of the routine biological examination at the Department. We chose the threshold of 5 mg/L as the cutoff between the high CRP group and the normal CRP group. This threshold was determined based on data from literature and similar studies [8].

2.6. Statistical Methods

Statistical analysis was performed using SPSS software version 19.0. The descriptive analysis consisted on a calculation of the absolute and relative frequencies for the qualitative variables, and of the positioning and dispersion parameters for the quantitative variables (mean, standard deviation). The normal distribution of variables was studied by the Kolmogorov-Smirnov test. In a bivariate analysis, the comparison of qualitative variables used the Pearson Chi2 statistical test and Fisher's if necessary. Multivariate binary logistic regression analysis was used to eliminate confounding factors and keep only those that are independently related to inflammation. Variables whose association was significant at the 20% threshold in bivariate analysis were included in a multivariate model. The variables retained in the final model were selected using a stepwise forward method with an entry threshold of 0.2 and an exit threshold of 0.05. The Hosmer Lemeshow test was used to examine the quality of the final logistic regression model. The threshold of significance was retained for a p <0.05.

3. Results

3.1. Socio-Demographic Characteristics

Total of 154 subjects were included in the study. The mean age was 27.98 ± 11.34 years with extremes ranging from 18 to 61 and consisted only of men. All patients have a history of hospitalization in a psychiatric hospital and no patient had a somatic comorbidity due to the exclusion criteria (Table 1).

Table 1. Demographic characteristics of the study subjects.

	CRP≤5mg/L N=102	CRP>5mg/L N= 52	p-value
Age in years, mean (SD)	28,53 (7,985)	26,9 (6,46)	0,12
Residency			
Rural, n (%)	20 (19,6%)	13 (25%)	0,44
Urban, n (%)	82 (80,4%)	39 (75%)	
Occupation, n (%)			
Unemployed	90 (88,2%)	42 (80,8%)	0,21
Employed	12 (11,8%)	10 (19,2%)	
Education, n (%)			
Pimary and secondary	98 (96,1%)	52 (100%)	0,017
High and university	4 (3,9%)	0	
Lower socio economic status	69 (67,6%)	34 (65,4%)	0,77

3.2. CRP Levels and Clinical and Biological Features of Schizophrenia

Table 2 shows the associations between clinical and biological characteristics of schizophrenic patients and the rate of CRP.

Table 2. Study of the association between CRP level and clinical and biological characteristics of schizophrenia.

	CRP ≤5mg/L N=102	CRP>5mg/L N=52	p-value
Age of schizophrenia onset, mean (SD)	22,45 (3,811)	21,21 (2,919)	0,027
Duration of illness, (years) mean (SD)	6,08 (6,174)	5,79 (4,964)	0,76
Smoking status			
Yes, n (%)	77 (75,4%)	48 (92,3%)	0,015
No, n (%)	24 (23,5%)	4 (7,7%)	
Cannabis Use			
Yes, n (%)	51 (72,9%)	19 (27,1%)	0,12
No, n (%)	31 (59,6%)	21 (40,4%	
Clinical measures			
Total PANSS, mean (SD)	64,01 (7,744)	78,81 (11,244)	0,0001
PANSS positive, mean (SD)	21,94 (4,807)	27,52 (5,731)	0,0001
PANSS negative, mean (SD)	12,74 (2,725)	14,44 (2,967)	0,0001
PANSS general psychopathology, mean (SD)	29,15 (5,33)	35,35 (8,510)	0,0001
PANSS depression, mean (SD)	5,96 (1,482)	6,29 (1,753)	0,25
Laboratory parameters			
White blood cells (10^3/ml), mean (SD)	8,241 (1,0547)	8,249 (1,4734)	0,97
Neutrophil cells (10^3/ml), mean (SD)	5,389 (0,9504)	5,309 (1,5837)	0,73
Lymphocyte cells (10^3/ml), mean (SD)	1,197 (0,5095)	1,712 (0,7635)	0,0001
Aggression measures			
PANSS excitement, mean (SD)	8,76 (3,591)	18,33 (3,833)	0,0001
Restraint during hospitalization n (%)	17 (16,7%)	47 (90,4%)	0,0001
Suicidal ideation or suicide attempt n (%)	6 (5,9%)	13 (25%)	0,001
Injectable treatment, n (%)	12 (11,8%)	48 (92,3%)	0,0001

3.3. Logistic Regression

Table 3. Binary logistic regression model with CRP> 5mg / L.

	B	χ2	p	OR	OR (IC à 95,0%)	
Education level	,978	,425	,514	2,660	,140	50,357
Substance use	,871	,249	,618	2,389	,078	73,056
Age of schizophrenia onset	-1,788	1,458	,227	,167	,009	3,047
Lymphocte cells	3,383	6,267	,012	29,458	2,084	416,323
Total PANSS	,443	4,392	,036	1,558	1,029	2,357
PANSS Positive	-,398	2,479	,115	,671	,409	1,102
PANSS Negative	-,549	3,197	,074	,578	,316	1,054
PANSS General psychopathology	-,407	3,309	,069	,666	,429	1,032
PANSS EXC	,622	5,585	,018	1,863	1,112	3,121
Restraint during hospitalization	-2,348	1,183	,277	,096	,001	6,579
Suicidal ideation or suicide attempt	-,497	,064	,801	,609	,013	28,902
Injectable treatment	-1,800	,690	,406	,165	,002	11,545
Constante	-8,794	1,432	,231	,000		

β: Bêta constante, χ2: Wald, p: the threshold of significance for the Wald test, OR: Odds Ratio.

A binary logistic regression of CRP> 5mg/L was performed to evaluate the coefficients of variation (Table 3). We found that the variables: Lymphocyte count, total PANSS score, PANSS excitement score were independently associated with a CRP> 5 mg/L.

4. Discussion

Our study aimed to confirm the hypothesis that hospitalized patients with schizophrenia with elevated CRP would be more aggressive.

We chose in our study four clinical parameters as indicators of aggressive behavior in schizophrenic patients:

PANSS Score Excitement, use of physical restraint during hospitalization, presence of suicidal ideation or suicide attempts, and administration of injectable medications. As a result, we found a positive correlation between the four aggression indicators and the increase in CRP.

4.1. Panss Exc

In our study, the PANSS EXC score was 10 points higher in the high CRP group compared to the other group. Patients with high CRP required five times more the use of mechanical restraint. These two results are consistent with the Barzilay study, which retrospectively compared 213 schizophrenic patients with elevated CRP with 156 schizophrenic patients with normal CRP. This study found a positive relationship between the PANSS EXC score and the high CRP score, the score was two points higher and the use of restraint was multiplied by 2.48 in the high CRP group [14].

Another study that assessed the clinical and biological characteristics of agitated schizophrenic patients (N = 32) compared to a healthy control group (N = 42) concluded that the patients with elevated CRP levels have more severe clinical symptoms [15]. This difference could be explained by several factors: the delay of care and demand for care, the complexity on the access to psychiatric care, poor family care and especially in our study by the presence of substance abuse.

4.2. Injectable Treatment and Use Physical of Restraint

The administration of injectable treatment was present in 92.5% of patients with a high CRP, concord with the use of physical restraint. These results ask the efficiency of communication techniques and the quality of the therapeutic alliance of carers vis-à-vis these patients.

4.3. Suicidal Ideation and Suicide Attempts

The presence of suicidal ideation or suicide attempts was five times higher in schizophrenic patients with high CRP. Several studies revealed the association of an inflammatory state characterized by the elevation of inflammatory markers at central and peripheral level with suicidal ideation and suicidal act [16, 17]. However, suicidality requires the use of specific scales as well as an analysis of the context and meaning of the act during the suicide attempt to have a better understand this pattern.

4.4. CRP and Psychopathological Signs of Schizophrenia

We found that patients with elevated CRP had a total PANSS score and scores of subscales: PANSS positive and negative significantly elevated compared to the normal CRP group. The exploration of psychopathological signs of schizophrenia in relation to biological markers was subject to some studies with controversial results [18]. Thus, Fan and all showed a significant rise in PANSS scores and PANSS subscale scores except for positive PANSS by comparing two groups of patients with schizophrenia according to the CRP rate [19]. Although In an Egyptian study of 200 patients with schizophrenia after CRP measurement and PANSS clinical assessment, a CRP elevation was accompanied by a high score of total PANSS and PANSS sub-scales [20]. Nonthelesse Joseph and all study of 88 patients found no significant relationship between CRP and clinical signs of schizophrenia [21].

Otherwise, Dickerson and all found that high CRP levels were related to greater cognitive impairment and did not find a relationship between CRP and the severity of psychopathological symptoms [22]. Similarly, in Kuwaiti study of 207 patients, CRP was not significantly associated with the severity of clinical signs, but with the presence of catatonic syndrome [23].

4.5. CRP and Depression in Patients with Schizophrenia

Our study found no significant relationship between the PANSS depression score and the CRP level and no patients in both groups were on antidepressants. This result consists with the Barzilay and all study with an average of 8.77 for the scale score and an average of 6.07 for our study [14]. However, several studies have highlighted the elevation of inflammation markers in depressed patients with suicidal ideation [16, 17]. The Valkanova and all meta-analysis which included eight studies for CRP (14832 participants) and three studies for IL-6 (3695 participants) showed a significant association between the elevation of these two biological markers, especially CRP with the presence depression and the severity of depressive symptoms [24]. This result should be interpreted with caution as the PANSS depression items could be confused with the negative symptoms of schizophrenia or the side effects of neuroleptics. It would be better to combine two or three scales of depression for more reliable results.

4.6. CRP and the Other Biological Parameters

For the other biological parameters, we did not find any significant difference between the two groups concerning the number of white blood cells, whereas a very significant association was found between the lymphocyte number and the CRP level, thus the Lymphocyte count was

independently associated with CRP> 5 mg/L with RRs estimated by the following Odds Ratio (29.45, 95% CI: 2.08 and 416.32). The study by Pan and all found a significant difference between the number of white blood cells and the CRP level without evaluation of the number of lymphocytes [15]. The study of Barzilay and all studied several biological parameters and found a positive correlation between CRP and white blood cell count, lymphocyte cell count, neutrophil count, albumin and platelet count [14]. However, other studies did not reproduce the same results [19, 20]. The meta-analysis of Miller and all provides more clarification and proposes that CD4, CD8, and CD4 / CD8 significantly increase during a first psychotic episode, that the ratio CD4 / CD8 appears as a state marker seen that it is normalized after treatment with neuroleptics while the CD56 would be a marker trait since it remains high even after treatment [25].

4.7. Perspectives

Current research in psychiatry is increasingly interested in biological parameters in search of a possible links between clinical signs and biological indicators, the study we conducted to our knowledge would be the first in Morocco that treats inflammation, markers and schizophrenia and among the few that have focused specifically on the aggressive behavior of relapsing schizophrenic patients in relation to a biological marker. These results would be interesting to the extent of a reflection around a staging of schizophrenic patients according to the likely risk of aggression and acting out, and thus to adapt the medical management of each patient according to his potential to violence. Indeed recent studies have relied in the presence of inflammatory mechanisms to propose new therapeutic classes in combination with neuroleptics, Muller and all reported that the use of anti-inflammatory drugs steroids Celexocib in combination with risperidone for 5 weeks for the treatment of patients with relapsing-reactive schizophrenia can improve the PANSS score [26-29], other studies with the same molecule or with aspirin showed the same results [30, 31]. On the other hand, the study of Rapaport and Muller with Celexocib and two clinical trials with minocycline found an effect limited to the acute phase and which is not reproducible and not durable [32-34]. These therapeutic data confirm the importance of stratifying and codifying the management of patients according to the institutional or ambulatory framework, the clinical and biological profile of schizophrenic patients.

4.8. Limitations

There are limits to our research: the absence of female schizophrenic patients, we can not be certain that the elevation of CRP is specific to the aggression of schizophrenic patients, it could be a common phenomenon of relapse or the acute phase regardless the initial psychiatric pathology.

5. Conclusion

Schizophrenia remains in our context the most frequent psychiatric disorder at the hospital level with a long history of stigmatization based on behavioral disorders, violence and hetero-aggressive behavior that may exist during the evolution of the disease and at the time of relapses. Our study highlighted several findings: First, hospitalized patients with schizophrenia who have a high CRP have significantly more aggressive behaviors. Second, the CRP level is also correlated with the severity of the psychopathological symptoms assessed by the PANSS scale. Third, the number of lymphocyte cells significantly follows the rise in CRP levels. Fourthly, the predictive factors for CRP elevation in schizophrenic patients after logistic regression are: the total PANSS score, the general PANSS score, and the number of lymphocyte cells.

Thus, these results confirm the role played by inflammation and immunity in the appearance of aggressive behavior in schizophrenic patients and highlight the interest of the CRP assay at the admission of patients as an indicator of aggression in hospitalized patients with schizophrenia.

Conflicts of Interest

The authors declare that they have no competing interest.

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