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## ARTICLE ORIGINAL

# IMMUNO-INFLAMMATORY EVALUATION IN PATIENTS WITH PSYCHIATRIC DISORDERS

Evaluation immune-inflammatoire des patients atteints des troubles psychiatriques

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### MOTS CLÉS

Auto-antibodies ;  
Psychosis ;  
Inflammatory ;  
Biomarkers.

### Abstract

The molecular mechanisms underlying psychiatric disorders are complex, involving interactions between genetic, environmental, inflammatory, and epigenetic factors, as well as dysfunctions at the level of neurotransmitters, synapses, and neural networks. Currently, neuroinflammation plays an increasingly recognized role in the development and worsening of psychiatric disorders such as depression, schizophrenia, and anxiety disorders. This chronic inflammation can disrupt the normal functioning of the brain, affecting neural circuits and contributing to symptoms specific to each disorder.

This study aims to evaluate the link between psychotic disorders and immuno-inflammatory processes. It is based on the analysis of 95 patients with psychiatric disorders, compared to 30 healthy controls. The results highlight a significant increase in inflammatory markers and a notable presence of autoantibodies in a subset of patients. These findings suggest the existence of an immune-mediated subtype of psychosis, paving the way for a personalized therapeutic approach.

In summary, inflammation is increasingly recognized as an important factor in psychiatric disorders. Understanding of the underlying mechanisms of inflammation will help improve patient management and quality of life.

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## Introduction :

Inflammation, long integrated as part of the innate immune response and considered a defensive reaction of the body [1], is now increasingly recognized as playing a key role in the emergence and development of various psychiatric disorders such as depression, anxiety, and schizophrenia [1, 2, 3, 4]. The concept of immunopsychiatry, as an emerging discipline, studies this complex link, to explore possible therapeutic strategies, particularly those based on modulation of the immune system to achieve better control of psychiatric pathologies, especially treatment-resistant forms [5].

Over the past few years, many studies have highlighted a close association between immuno-inflammatory processes and the onset of psychiatric disorders, particularly psychoses [5]. In addition, several observations have established a strong link between autoimmune diseases (AID) and psychiatric disorders, showing not only an increased risk of mental health, but also that psychological factors may play a role in the development or exacerbation of AID [5, 6].

The pathophysiology of the concept AID, which often exhibit a higher prevalence of psychiatric symptoms, suggests a pathogenic interaction between systemic inflammation and brain dysfunction [5, 6]. This relationship is reinforced by the identification of a shared immunogenetic background and by the presence of autoantibodies (auto-Abs) in the serum of some psychotic patients [7, 8]. During neuroinflammation, pro-inflammatory cytokine levels increase significantly, including interleukin-6 (IL-6), which has a proven neurotoxic role. This increase is observed more markedly in individuals experiencing their first psychotic episode compared to healthy subjects. Elevated levels have been found not only in peripheral blood but also, surprisingly, in cerebrospinal fluid, indicating that inflammation is also present in the brain [9, 10]. Similarly Post-mortem studies have also shown significantly increased levels of IL-6-inducing proteins and NF- $\kappa$ B in the brains of patients with schizophrenia, indicating activation of the inflammatory network within the brain [10, 11].

This inflammation can alter the functionality of neural circuits responsible for emotions and behavior, leading to depressive syndromes observable through functional imaging (fMRI), particularly in patients with elevated levels of C-reactive protein (CRP) [12]. This disruption of communication between different regions can, by itself, cause decreased energy, fatigue, anhedonia, slowed thinking, and even difficulty following conversations or remembering things [12].

In addition, Recent studies have also identified new auto-Abs targeting specific brain receptors, especially in subgroups of patients with

schizophrenia or other psychotic disorders, which can in some cases impair synaptic plasticity [6, 9]. These auto-Abs may serve as stratification biomarkers, offering not only a better understanding of the underlying pathophysiological mechanisms but also the possibility of developing targeted therapeutic strategies [8].

Today, research increasingly indicates that major psychiatric illnesses such as schizophrenia, depression, or bipolar disorders should also be considered immuno-inflammatory diseases. It turns out that all of these diseases do not only reside in the brain, but they have a systemic component, that is to say, the immune system. [6, 7, 8, 9].

Within this context, the present study aimed to assess the frequency of autoantibodies in a population of patients with psychiatric disorders, study the inflammatory status of these patients through CRP measurement and serum protein electrophoresis, and evaluate the clinico-biological correlation between inflammation, autoimmunity, and clinical expression.

## Material and methods

This was a prospective descriptive study conducted between 2020 and 2024 at the Immunology Unit of the Department of Medical Biology, Blida University Hospital. Patients included in our study were recruited from the Psychiatry Departments (EHS Frantz Fanon), the Neurology Department (Blida University Hospital), and other hospitals across different regions of the country. Psychiatric disorders were diagnosed according to the DSM-5 classification criteria.

Some patients also underwent consultations in the Rheumatology Department of the "Ibrahim TERICHINE" Hospital and the Internal Medicine Department of Blida University Hospital.

Out of 125 recruited patients, 95 were selected for the study, all presenting syndromic psychiatric disorders with somatic rheumatologic or neurological manifestations. Additionally, 30 healthy controls were included, with no history of psychiatric, inflammatory, or autoimmune disorders.

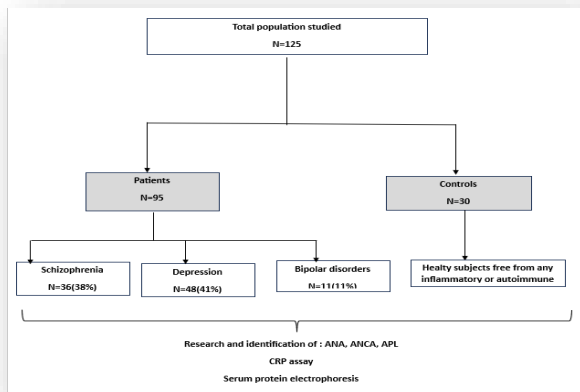


**Figure 1.** Flow diagram of study population recruitment

The subjects in our study population (patients and controls) benefited from :

Inflammatory profile : Measurement of C-reactive protein (CRP) and serum protein electrophoresis to detect acute inflammatory syndrome (AIS), chronic inflammatory syndrome (CIS), and chronic progressive inflammatory syndrome (CPIS).

Autoimmunity profile (INOVA® kit) : Detection and identification of antinuclear autoantibodies (ANA) using indirect immunofluorescence (IIF) and ELISA techniques. Additional testing included anti-neutrophil cytoplasmic antibodies (ANCA), anti-thyroid peroxidase antibodies (anti-TPO), anti-thyroglobulin antibodies (anti-Tg), and antiphospholipid antibodies.

#### STATISTICAL ANALYSIS

Descriptive statistics: Quantitative data are expressed as mean  $\pm$  standard deviation with ranges. Qualitative variables are summarized as number and/or percentage of patients.

Analytical statistics: Data analysis was performed using GraphPad software. The Hardy-Weinberg equilibrium was assessed using the Chi-square test. Odds ratios (OR) and 95% confidence intervals were calculated using Fisher's exact test. Yates' correction was applied for small samples. A p-value  $<0.05$  was considered statistically significant.

## Résultats

Characteristics of the study population by sex and age

We observed a slight female predominance in our study population, with a sex ratio of 0.86 M/F (44 men [55%] vs. 41 women [45%]).

The mean age of our study population was  $53.23 \pm 13.78$  years [42–80], While stratified by psychiatric pathology, the mean age was higher in patients with schizophrenia compared to those with depressive syndrome and bipolar disorders (respectively:  $56.21 \pm 15.02$  [55–80] vs.  $51.98 \pm 13.58$  [42–61] vs.  $47.26 \pm 4.78$  [43–51]).

In healthy controls, demographic characteristics were 24F/6M with a mean age of  $43.07 \pm 14.80$  years [20–76]. (Figures 2 and 3)

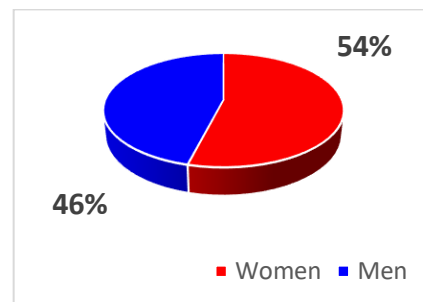


**Figure 2.** Distribution of patients by sex

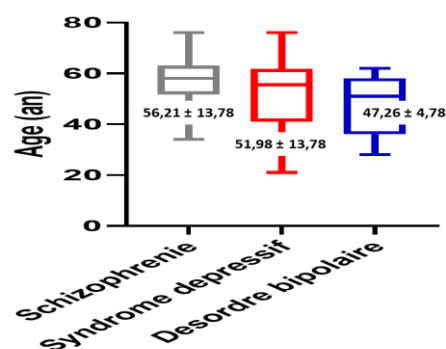


**Figure 3.** Age distribution of patients with psychiatric disorders

#### Distribution of patients according to CRP levels

Analysis of CRP levels, a classical marker of systemic inflammation, revealed elevated values in 46 patients (48%). A significant difference was found between patients with psychiatric disorders and the control group ( $17.44 \pm 5.02$  g/L vs.  $4.1 \pm 1.3$  g/L,  $p = 0.002$ , OR = 3.1).

By psychiatric diagnosis, mean CRP concentrations were significantly higher in patients with schizophrenia compared to those with depression and bipolar disorders ( $21.19 \pm 12.3$  g/L vs.  $18.22 \pm 10.7$  g/L vs.  $9.63 \pm 4.7$  g/L,  $p = 0.002$ ). ( See Figure 4)

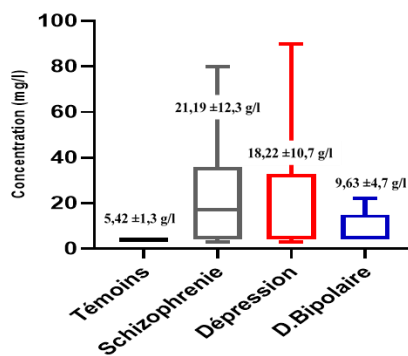


**Figure 4.** Distribution of CRP levels among patients by diagnosis (Schizophrenia, Depression, Bipolar Disorder).

### Distribution of patients according to serum protein electrophoresis profile

The electrophoretic profile in patients with psychiatric disorders revealed notable inflammatory abnormalities compared to the control group.

In controls, all individuals (100%) showed a normal electrophoretic profile, consistent with the absence of inflammatory pathology.

In parallel, we observed, depending on the psychiatric pathology, the serum electrophoretic profile was inflammatory in 35% of patients with schizophrenia (23% CIS, 10% AIS and 2% PCIS), 45% of patients with depressive symptoms (26% AIS, 11% CPIS and 8% CIS), and 21% of patients with bipolar disorders (13% CIS, 6% AIS and 2% PCIS). (See Figure 5)

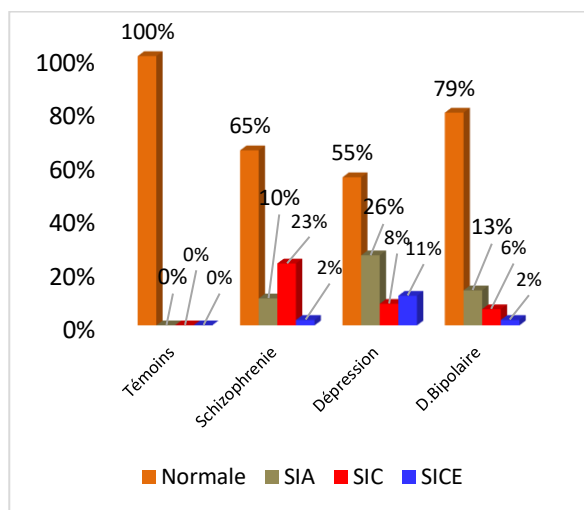


**Figure 5.** Distribution of serum electrophoretic profiles by diagnosis (Schizophrenia, Depression, Bipolar Disorder).

### Distribution of patients according to suspected autoimmune diseases (AID)

Symptoms suggestive of AID were remarkably more frequent in patients with depressive

symptoms (33/48; 68%), followed by schizophrenia (56%) and bipolar disorders (27%).

**Table 1.** Distribution of patients according to suspected autoimmune diseases

|                                | Suspected AID* | No suspected AID |
|--------------------------------|----------------|------------------|
| Healthy controls (N = 30)      | 0              | 30 (100%)        |
| Schizophrenia (N = 36)         | 20 (56%)       | 16 (44%)         |
| <b>Depression (N = 48)</b>     | 33 (68%)       | 15 (32%)         |
| Bipolar disorders (N = 11)     | 3 (27%)        | 8 (83%)          |
| <b>Total patients (N = 95)</b> | 56 (59%)       | 39 (41%)         |

\*Based on clinical and biological signs such as joint pain, asthenia, alopecia, fever, rapidly developing obesity, anemia, leukopenia, thrombocytopenia, etc.

### Distribution of patients according to ANA detection

The search for ANA revealed variable frequencies of positive cases according to the type of psychiatric disorder, with an estimated positivity rate of 75% in patients with depressive symptoms (49% with significant titers), 50% in patients with schizophrenia (30% with significant titers), and 36% in patients with bipolar disorders (13% with significant titers). (See Figure 6)

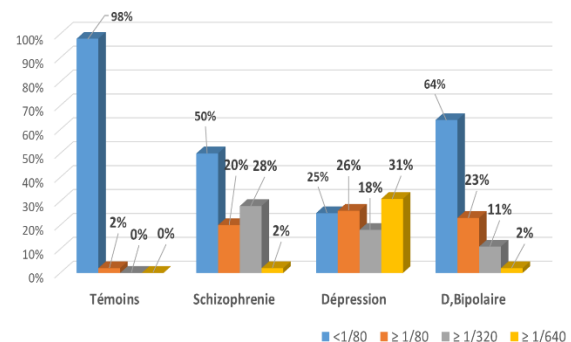


**Figure 6.** Distribution of ANA positivity by diagnosis

### Distribution of patients according to ANA target specificity

In our study, we found that 15 out of 95 patients were diagnosed with SLE, with the presence of multiple targets including anti-native DNA, anti-Sm, and anti-ribosomal antibodies. At lower frequencies, other diagnoses were established: 10 cases of autoimmune thyroiditis, 8 cases of primary or secondary antiphospholipid syndrome (presence of anti-cardiolipin and anti-β2GP antibodies), 4 cases of ANCA-associated vasculitis, 2 cases of Sjögren's syndrome (presence of anti-SSA/SSB autoantibodies), and one case of scleroderma (presence of anti-Scl70 autoantibodies). Interestingly, autoimmune

diseases were more pronounced among patients with depressive syndrome, with 10 confirmed cases of SLE (with or without associated APS) and an equal number of autoimmune thyroiditis.

**Table 2. Distribution of patients according to autoantibody specificity and AID diagnosis**

| Identified targets (autoantibodies) | Schizophrenia<br>N = 36 | Depression<br>N = 48 | Bipolar<br>D<br>N = 11 | Systemic<br>diagnosis |
|-------------------------------------|-------------------------|----------------------|------------------------|-----------------------|
| Anti-DNA natif                      | 5                       | 5                    | 1                      | SLE                   |
| Anti-Sm,                            | 1                       | 3                    | 1                      | SLE                   |
| Anti-Sm/RNP,                        | 0                       | 2                    | 0                      | SLE                   |
| Anti-RNP                            | 0                       | 1                    | 0                      | Mixed                 |
| Anti-SSA/Ro                         | 0                       | 1                    | 0                      | Mixed                 |
| Anti-SSB,                           | 0                       | 1                    | 0                      | SS                    |
| Anti-Sc170,                         | 0                       | 1                    | 0                      | SS                    |
| Anti-Jo-1,                          | 1                       | 5                    | 1                      | SLE                   |
| APL                                 | 2                       | 6                    | 0                      | PM                    |
| Anti-TPO                            | 1                       | 5                    | 4                      | SAPL                  |
| Anti-Ig                             | 0                       | 2                    | 2                      | AIT                   |
| ANCA                                | 0                       | 1                    | 3                      | AIT                   |
|                                     |                         |                      |                        | Vasculitis            |

## Discussion

Autoimmune diseases (AID) with psychiatric manifestations mainly affect women, with an incidence peak during adolescence and early adulthood, although they may occur at any age. This predominance appears to be multifactorial, involving genetic predisposition to develop inflammatory rheumatism with psychiatric expression, in an environment favoring viral infections [6, 7, 13, 14]. AID can manifest with a variety of mental disorders such as mood disorders (depression, anxiety), psychotic disorders (psychosis, delusions), neurodevelopmental disorders (autism spectrum disorders, attention deficit hyperactivity disorder), obsessive-compulsive disorders, fatigue, sleep disturbances, and finally the pains, all of which may influence the perception of symptomatology [9, 15].

Several studies have confirmed this female predominance [6, 13, 14], and have identified the coexistence of multiple comorbid factors, including genetic predisposition common to both AID and psychiatric disorders, stress (trauma, grief, separations), and the inflammatory background characteristic of AID [6, 15].

In our study, we also observed a female predominance across the three groups of pathologies despite the relatively small sample size, regarding age, our patients tended to be older, suggesting that the development of psychiatric symptoms may be linked to chronic exposure to systemic inflammatory flares. A more in-depth etiological investigation would be necessary to identify the main factors underlying this chronic inflammation.

With regard to biological inflammatory markers in autoimmune-related psychotic disorders, CRP remains the most accessible biomarker of inflammation in medical biology services.

Produced by the liver, elevated CRP indicates acute or chronic inflammation [16, 17]. In addition to the existence of a link between AID, elevated CRP, and the risk of psychiatric symptoms, it seems that the chronicity of inflammation that characterizes AIDs can affect the central nervous system, thus increasing the risk of psychiatric disorders such as depression, anxiety, and even psychotic symptoms. [16, 17, 18].

Several studies have also demonstrated associations between increased cytokines and inflammatory proteins such as CRP, and that these biomarkers were associated with risks of occurrence of deficits in verbal memory, working memory, processing speed, mental flexibility and reasoning [19, 20, 21]. Most of these studies focused specifically on inflammatory abnormalities and cognitive dysfunction in schizophrenia [16, 17, 21, 22].

In our cohort, CRP values were variable, reflecting heterogeneity of the inflammatory response. Although the mean CRP was slightly lower than in schizophrenia patients, the inflammatory profile remains notable across all three groups studied.

The chronological assessment of inflammatory syndromes in our patients, through serum protein electrophoresis, allowed us to identify underlying inflammatory activity in psychotic disorders with autoimmune features. However, psychiatric symptoms can be complex and multifactorial causes, and electrophoresis is only one part of a broader diagnostic workup. This examination can also screen for complications such as renal involvement in neurolupus [23, 28].

Other research teams have confirmed the usefulness of serum protein electrophoresis in detecting inflammation and renal involvement since the method was first described, and it is now mainly recommended for diagnosing monoclonal gammopathies [23, 28].

Others have mentioned, in particular, alterations in social cognition and heightened emotional reactivity that may be aggravated by an underlying inflammatory background. This supports the possible existence of a specific inflammatory phenotype, which may be correlated with behavioral dimensions such as impulsivity or violence [23, 28].

In our population, sensitivity in the identification of inflammatory syndromes has not been shown, this can be explained by the fact of the clinical entity with neurological expression, which requires an electrophoretic study on the cerebrospinal fluid (CSF), in order to better understand the inflammatory mechanisms at the level of the nervous system

After evaluating inflammation, we examined the risk of triggering a breakdown in immune tolerance. According to the literature, this risk is variable, estimated between 45% and 55% for the occurrence of psychosis in AID and vice versa [16].

In our population, a variable frequency of positive ANA titers was noted depending on the psychiatric pathology, higher in patients with depression and schizophrenia. This strongly suggests autoimmune pathologies, compared to 2% in our population of healthy controls. Notably, 15 ANA-positive patients exhibited one or more antigenic specificities. This may be explained by multiple factors contributing to neuropsychiatric autoimmune symptomatology, such as medications that induce ANA production, concurrent active infections notably viral or *Mycoplasma pneumoniae*, and hematologic malignancies [14].

The literature remains contradictory. Some studies have established significant associations between connective tissue diseases and autoimmune enteropathies on the one hand, and autoimmune psychoses on the other [24, 25, 26, 27]. Others have found no significant results [28]. The most widely accepted hypothesis is the coexistence of low-grade inflammation and autoimmunity, which, through various molecular and psychological mechanisms, may trigger genuine psychotic syndromes in predisposed individuals [28].

The value of immunopsychiatric analyses will become more evident with the exploration of antineuronal antibodies in larger samples, to clarify the neuronal processes underlying autoimmune psychoses.

In our cohort, neuro-lupus, antiphospholipid syndrome, and autoimmune thyroiditis were the autoimmune diseases most associated with psychosis, particularly schizophrenia and depressive syndromes, and this does not allow us to confirm the link like some research teams [27] or, on the contrary, to deny it like others [23, 24, 25, 29, 30].

Our results confirm the presence of significant inflammatory activation in patients with psychiatric disorders, especially schizophrenia and depression. Elevated CRP and the presence of autoantibodies suggest involvement of the peripheral immune system in the pathophysiology of these disorders. These findings are consistent with the growing body of literature emphasizing the role of pro-inflammatory cytokines and autoimmune processes in psychiatric symptoms. All the data from our study highlights importance of immuno-inflammatory mechanisms in the understanding of major psychiatric disorders. Elevated CRP, altered electrophoretic profiles, and the presence of auto-Abs in a significant proportion of patients indicate that a non-negligible subset of psychotic, depressive, and bipolar disorders may fall within an immunological framework.

Cross-referencing our results with recent studies, particularly those of Mezoued, Jeppesen, and Severance, it appears that inflammation is not merely an episodic marker but a persistent biological trait in some psychotic patients, particularly associated with negative symptoms,

treatment resistance, and atypical clinical forms [27, 28, 30].

These observations strengthen the case for early, targeted immuno-inflammatory screening in psychiatric disorders, aiming to stratify patients according to their inflammatory profile. Such an approach opens the way to personalized precision medicine, still insufficiently applied in this field, integrating immunomodulatory adjuvant treatments, still little used in psychiatry today.

Finally, further longitudinal and mechanistic research is needed to better characterize the links between peripheral inflammation, brain dysfunction, and clinical expression. Identifying reliable and reproducible biomarkers will ultimately enable the development of more precise and effective therapeutic strategies, tailored to each patient's biology.

## Conclusion

This study highlights the importance of integrating the evaluation of immuno-inflammatory markers into the management of psychiatric disorders. Such an assessment would allow better identification of patients with an immune-mediated form of psychosis, thereby justifying the use of adjunctive immunomodulatory therapies.

It is crucial that healthcare professionals remain attentive to psychiatric symptoms in individuals with autoimmune diseases, as early screening and timely management can significantly improve patients' quality of life.

## Déclaration d'intérêts

The authors have no conflicts of interest to declare.

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