Cytokine profile among a sample of bipolar and schizophrenic patients: a comparative study

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Background
Bipolar disorder (BD) and schizophrenia are serious forms of mental illness which are considered to be complex and multisystemic conditions. Several lines of evidence point to the key role of immune dysfunction in both disorders, with recent reports citing abnormal blood levels of cytokines where the most obvious mechanism is a dysregulation of the balance of proinflammatory and anti-inflammatory cytokines.
Objective
The aim was to explore the presence of immune dysfunction in BD in comparison with schizophrenia and to compare them to apparently healthy control persons.
Participants and methods
This study was a cross-sectional study on 90 individuals (30 diagnosed as BD, 30 as schizophrenic, and 30 apparently healthy controls). Age matched and sex matched. They were assessed by general medical and neurological examination. Semistructured clinical interview for DSM-IV (SCIDI), positive and negative schizophrenia scale (PANSS) for the schizophrenia group, Yearsania rating scale (YMRS) for the bipolar group, and laboratory investigations include: serum interleukin (IL)1B level and serum IL6 level for the three groups.
Result
The mean serum IL1B level was found to be higher in the bipolar group than that of the control group and schizophrenia group .The mean serum IL1B level in the schizophrenia group was higher than that of the control group. The mean serum IL6 level was higher in the bipolar and schizophrenia groups than that of the control group. It was also found that serum IL1B showed a highly significant correlation with the duration of illness in the bipolar group, while serum IL6 showed a significance with the duration of illness in the bipolar and schizophrenia groups. In the bipolar group, significant correlation was found between IL6 and number of episodes, while in the schizophrenia group, a significant correlation was found between IL6 and age at onset of illness and number of episodes.
Conclusion
There is mounting evidence of increased immune markers, particularly proinflammatory cytokines in BD and schizophrenia patients. So, identifying the biomarkers could represent new tools which could help to improve diagnosis and find prognostic markers which offers great promises toward a better understanding of the etio-pathological mechanisms involved in BD and schizophrenia, and for the development of prevention and personalized treatments.

Keywords:
biomarkers, bipolar disorder, cytokines, interleukins 1B, interleukins 6, immune dysfunction, personalized medicine, schizophrenia, theranostic biomarkers

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Introduction

Bipolar disorder (BD) and schizophrenia are serious forms of mental illness that significantly impact a person's mood and functioning with the onset of symptoms occurring most frequently during late adolescence or early adulthood (Dickerson *et al.*, 2017). For several decades both schizophrenia and BD have been considered as distinct clinical entities. However, they share common biological features, such as brain changes in cases of long illness duration and alterations in inflammatory pathways (Gibney and Drexhage, 2016).

Traditionally, the brain has been considered as an area without contact with immune mediators, protected by the blood–brain barrier (Hatata and Attlah, 2009). However, in this work, together with the various studies reported, it may be of value to say brain tissue is able to engender immune processes and be influenced by them.

In recent years, the role of an altered immune system in the etiology of major psychiatric disorders has become more apparent, as studies have demonstrated that some patients with major psychiatric disorders exhibit characteristic signs of immune dysregulation. Furthermore, many psychiatric disorders are also accompanied by chronic medical conditions related to immune dysfunction such as autoimmune diseases, diabetes, and atherosclerosis Yamagata *et al*. (2017). It was also found that there is an increased risk of general medical comorbidities in patients with BD and schizophrenia with evidence of elevated systemic inflammation suggesting that 'immune dysfunction may be an important mechanistic link between BD, schizophrenia, and metabolic-inflammatory **c**omorbidities' (Greenberg, 2017).

Moreover, the risk for schizophrenia increased by prenatal and perinatal exposure to a number of adverse environmental factors including certain infections, maternal stress, malnutrition, and maternal medical complications (Malaspina *et al*., 2013). Individuals with schizophrenia also tend to be more vulnerable to infections, and that mortality from infectious disease is significantly higher in patients with schizophrenia than in the general population (Müller and Schwarz, 2016). Environmental factors such as childhood traumatic events, Praecox 'stressors' are thought to be associated with overexpression of specific polymorphisms (e.g. inflammatory cytokines) that would be responsible for immune dysregulation associated with schizophrenia and BD (Di Nicola *et al*., 2013).

Cytokines are a family of polypeptides that are essential to the immune system representing a marker of infectious and inflammatory conditions María *et al*. (2015). They play an important role during neurodevelopment at all stages from the differentiation of ectoderm into the neuroepithelium, to the renewal of neuroepithelial cells (Altamura *et al*., 2013).

Cytokines can be classed as proinflammatory, such as interleukin-1 (IL1), IL6, IL8, and tumor necrosis factor or anti-inflammatory, such as IL2, IL4, IL10, and IL13(Kronfol and Remick, 2014).

Proinflammatory cytokines, such as IL1β and IL6 have unique and specific actions on neurons and circuits within the central nervous system. They also have an effect on neurotransmission, memory, glucocorticoid function, as well as behaviors relevant to psychiatric disorders (Jones and Thomsen, 2013).

Biological markers such as cytokines may predict the outcome in BD and schizophrenia and help identifying at-risk individuals in preclinical stages which may facilitate new understanding of mental disorders and potentially provide new insight into treatment-resistant patients (Lakhan and Vieira, 2015).

Aim

The current study aimed at assessment of immune dysfunction among a sample of bipolar and schizophrenic patients and to compare them with apparently health controls.

Participants and methods

This is a cross-sectional case–control comparative study. It included three groups: the bipolar group, which included 30 men and women aged 18–60 years from the outpatient clinic in Al-Zahraa University Hospital, Cairo, Egypt, who were diagnosed as BD according to the DSM-IV-TR criteria ; the schizophrenia group, which included 30 men and women aged 18–60 years from the outpatient clinic in Al-zahraa University Hospital, Cairo, Egypt, who were diagnosed as schizophrenia according to the DSM-IV-TR criteria. All patients were kept on their psychotropic medication and the control group included 30 participants (men and women) aged 18–60 years who are apparently healthy without recent or past psychiatric disorder and with no family history of psychiatric disorder. They were collected from the medical and paramedical staff working in Al-Zahraa University Hospital. In a recent study, we exclude participants with recent infection, autoimmune disease, acute or chronic physical diseases, systemic, endocrine, immune disorders, infections, allergies history of obesity or undernutrition with recent weight loss, and pregnancy or breastfeeding. Age, sex, education, and social standard matched in the three groups. The consent: this study was approved by the Ethics Committee of Faculty of Medicine (Girls), Al-Azhar University. A formal consent was obtained from the patients and their caregivers after full discussion of the study rational. Participants in the study were informed that the study is totally free and voluntary, and that it does not imply a direct benefit for him/her, although data obtained could be used for the benefit of other patients. Procedures: all patients and control cases were subjected to the following: Semistructured interview that gathered general sociodemographic data And complete psychiatric history including past history, family history, and mental state examination. Laboratory investigations

for measuring serum IL1B and IL6; the blood samples have been taken from the antecubital vein into a vacutainer and they were left at room temperature for 1 h to leave time for the blood to clot. Serum and blood cells were separated by centrifugation (15 min, 3000 rpm). Serum samples were stored at −80°C until IL1B and IL6 measurements were made. IL-1β or IL-6 ELISA Kit was based on standard sandwich enzyme-linked immune-sorbent assay technology. A monoclonal antibody from mouse specific for IL-1β or IL-6 has been precoated onto 96-well plates. Standards and test samples are added to the wells, polyclonal antibody from goat specific for IL-1β or IL-6 is added subsequently and then followed by washing with buffer and unbound conjugates were washed away with buffer. A substrate was used to visualize enzymatic reaction. A blue color product changed into yellow after adding acidic stop solution. The density of yellow is proportional to thehuman IL-1β or IL-6 amount of sample captured in plate. For IL1B, the reference range was 3.9–250 pg/ml and for IL6 the reference range was 4.69–300 pg/ml. The following tools of assessment were used. First: Yearsania rating scale (YMRS), to assess the severity of manic episodes in the bipolar group, second: positive and negative schizophrenia scale (PANSS), to assess the severity of schizophrenia in the schizophrenia group.

Statistical methods

Data management and statistical analysis: data were collected, coded, revised, and entered into the Statistical Package for Social Sciences (IBM SPSS) SPSS software package version 20.0 (Armonk, NY: IBM Corp). The data were presented as number and percentages for qualitative data, mean, SD, and ranges for the quantitative data with parametric distribution and median with interquartile range for the quantitative data with nonparametric distribution. χ^2-Test was used in the comparison between two groups with qualitative data and Fisher's exact test was used instead of the χ^2-test when the expected count in any cell was found to be less than 5. Independent t-test was used in the comparison between two groups with quantitative data and parametric distribution and Mann–Whitney test was used in the comparison between two groups with quantitative data and nonparametric distribution.

Result

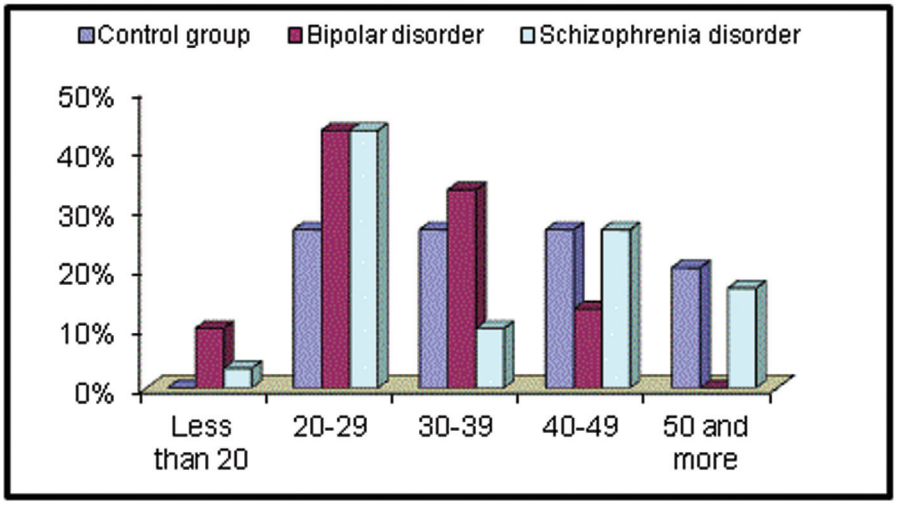
The results in the current study shows that the majority of the total sample lies in the range of 20–29 years and women represent the majority of the total sample (Figs 1 and 2).

Table 1 shows the distribution of marital status, occupation, and education among the total sample.

Table 2 shows that for IL1B: there is a high significant difference on comparing the bipolar group vs thevs control group. However, there is no significant difference on comparing schizophrenia group vs bipolar group or control group.

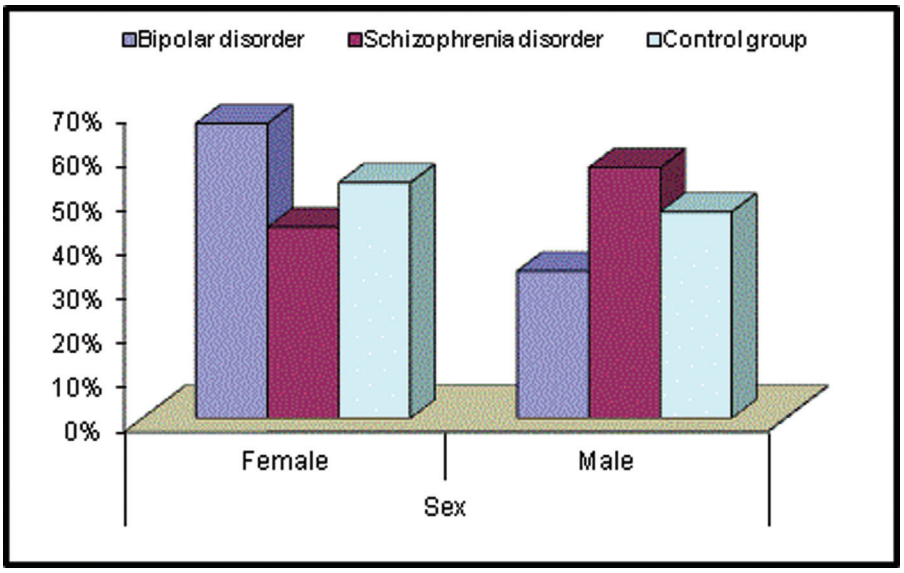
Table 3 shows that for serum IL6: there is a high significant difference on comparing the bipolar and schizophrenia groups vs the control group, while there was no significant difference on comparing the bipolar group vs the schizophrenia group.

Figure 1



Age distribution among the total sample.

Figure 2



Sex distribution among the total sample.

Table 1 Sociodemographic data of the total sample

Data	Control group (*N*=30) [*n* (%)]	Bipolar group (*N*=30) [*n* (%)]	Schizophrenia group (*N*=30) [*n* (%)]
Marital state			
Divorced	2 (6.7)	2 (6.7)	1 (3.3)
Married	23 (76.7)	16 (53.3)	11 (36.7)
Single	4 (13.3)	12 (40.0)	17 (56.7)
Widow	1 (3.3)	0 (0.0)	1 (3.3)
Occupation			
Manual worker	4 (13.3)	5 (16.7)	3 (10.0)
Not working	8 (26.7)	17 (56.7)	22 (73.3)
Professional worker	18 (60.0)	1 (3.3)	2 (6.7)
Student	0 (0.0)	7 (23.3)	3 (10.0)
Education			
<6 years	6 (20.0)	4 (13.3)	4 (13.3)
>12 years	7 (23.3)	8 (26.7)	9 (30.0)
6–12 years	17 (56.7)	16 (53.3)	11 (36.7)
Illiterate	0 (0.0)	2 (6.7)	6 (20.0)

Table 2 Serum IL1B among the total sample

Data	IL1B (mean±SD)
Control group	145.00±147.62
Bipolar group	316.97±338.37
Schizophrenia group	256.46±328.72

IL, interleukin. *t* Test 1: control vs bipolar=2.5, $P<0.05$. *t* Test 2: control vs schizophrenia=1.6, $P>0.05$. *t* Test 3: bipolar vs schizophrenia =0.7, $P>0.05$.

Table 3 Serum IL6 among the total sample

Data	IL6 (mean±SD)
Control group	134.73±196.93
Bipolar group	327.83±349.09
Schizophrenia group	355.37±347.45

IL, interleukin. *t* Test 1: control vs bipolar=2.6, $P<0.05$. *t* Test 2: control vs schizophrenia=2.9, $P<0.01$. *t* Test 3: bipolar vs schizophrenia =0.3, $P>0.05$.

Table 4 Mean score of PANSS and YMRS

	Mean±SD	Equivalence
Schizophrenia group		
PANSS positive subscore	27.17±15.13	3.88
PANNS negative subscore	23.07±12.05	3.29
Bipolar group		
YMRS	15.70±10.51	

PANNS, positive and negative schizophrenia; YMRS, young mania rating scale.

Table 4 shows that in the schizophrenia group the mean for positive subscore of the PANSS was equivalent to a moderate positive symptoms, while the mean for negative subscore of the PANSS was equivalent to mild negative symptoms and that the mean of YMRS in the bipolar group is 15.70 with SD ±10.51.

Table 5 shows that there are no significant correlation between serum IL1B level and age at onset of illness in both bipolar and schizophrenia groups.

Table 6 shows that in the schizophrenia group there is a high significant correlation between serum IL6 and age at onset of illness, while in the bipolar group there was no significant correlation.

Table 7 shows that there are no significant difference between serum IL1B level and number of episodes of illness in both bipolar and schizophrenia groups.

Table 5 Correlation between serum IL1B and age at onset of illnes

	Within normal			Above normal		Total	χ^2	*P* value
	<50 pg/ml	50–149 pg/ml	150–249 pg/ml	250–349 pg/ml	>350 pg/ml			
Bipolar group								
<20 years	4	1	0	0	5	10	11.96	>0.05
20–29 years	5	2	2	0	6	15		
30–39 years	2	0	0	1	2	5		
Total	11	3	2	1	13	30		
Schizophrenia group								
<20 years	2	1	0	0	1	4		
20–29 years	7	4	0	0	7	18		
30–39 years	3	0	0	1	1	5	15.7	>0.05
40–49 years	2	0	0	0	1	3		
Total	14	5	0	1	10	30		

Table 6 Correlation between serum IL6 and age at onset of illnes

	Within normal			Above normal		Total	χ^2	*P* value
	<50 pg/ml	50–149 pg/ml	150–249 pg/ml	250–349 pg/ml	>350 pg/ml			
Bipolar group								
<20 years	5	0	0	1	4	10		
20–29 years	7	2	0	0	6	15	8.65	>0.05
30–39 years	1	1	0	0	3	5		
Total	13	3	0	1	13	30		
Schizophrenia group								
<20 years	0	0	1	1	2	4		
20–29 years	7	1	1	0	9	18		
30–39 years	3	0	0	0	2	5		
40–49 years	2	0	0	0	1	3	27.7	<0.01
Total	12	1	2	1	14	30		

Table 7 Correlation between serum IL1B and number of episodes of illnes

	Within normal			Above normal		Total	χ^2	*P* value
	<50 pg/ml	50–149 pg/ml	150–249 pg/ml	250–349 pg/ml	>350 pg/ml			
Bipolar group								
1 episode	2	0	0	0	1	3		
2–5 episodes	5	1	2	1	6	15	19.5	>0.05
5–10 episodes	2	1	0	0	3	6		
>10 episodes	2	1	0	0	3	6		
Total	11	3	2	1	13	30		
Schizophrenia group								
1 episode	3	2	0	1	5	11		
2–5 episodes	7	2	0	0	2	11		
5–10 episodes	2	1	0	0	1	4	14.15	>0.05
>10 episodes	2	0	0	0	2	4		
Total	14	5	0	1	10	30		

Table 8 shows that in the schizophrenia group there is significant difference between serum IL1B level and number of episodes of illness while in the bipolar group there is no significant difference.

Table 9 shows that in the bipolar group there is high significant difference between serum IL1B level and duration of illness while in the schizophrenia group there is no significant difference.

Table 10 shows that in the bipolar group and the schizophrenia group there are significant differences between serum IL6 level and duration of illness.

Table 8 Correlation between serum IL6 and number of episodes of illnes

	Within normal			Above normal		Total	χ^2	*P* value
	<50 pg/ml	50–149 pg/ml	150–249 pg/ml	250–349 pg/ml	>350 pg/ml			
Bipolar group								
1 episode	1	0	0	0	2	3		
2–5 episodes	7	1	0	1	6	15		
5–10 episodes	2	1	0	0	3	6	12.94	>0.05
>10 episodes	3	1	0	0	2	6		
Total	13	3	0	1	13	30		
Schizophrenia group								
1 episode	5	0	0	0	6	11		
2–5 episodes	5	1	1	0	4	11		
5–10 episodes	1	0	1	0	2	4	22.99	<0.05
>10 episodes	1	0	0	1	2	4		
Total	12	1	2	1	14	30		

Table 9 Correlation between serum IL1B and duration of illnes

	Within normal			Above normal		Total	χ^2	*P* value
	<50 pg/ml	50–149 pg/ml	150–249 pg/ml	250–349 pg/ml	>350 pg/ml			
Bipolar group								
<1 year	0	1	0	0	2	3		
2–5 years	5	0	0	1	5	11	21.96	<0.01
5–10 years	3	1	2	0	4	10		
>10 years	3	1	0	0	2	6		
Total	11	3	2	1	13	30		
Schizophrenia group								
<1 year	3	1	0	0	3	7		
2–5 years	5	2	0	1	2	10		
5–10 years	3	1	0	0	2	6	9.7	>0.05
>10 years	3	1	0	0	3	7		
Total	14	5	0	1	10	30		

Table 10 Correlation between serum IL6 and duration of illnes

	Within normal			Above normal		Total	χ^2	*P* value
	<50 pg/ml	50–149 pg/ml	150–249 pg/ml	250–349 pg/ml	>350 pg/ml			
Bipolar group								
<1 year	0	0	0	1	2	3		
2–5 years	6	0	0	0	5	11		
5–10 years	5	1	0	0	4	10	17.79	<0.05
>10 years	2	2	0	0	2	6		
Total	13	3	0	1	13	30		
Schizophrenia group								
<1 year	3	1	0	0	3	7		
2–5 years	5	0	2	0	3	10		
5–10 years	2	0	0	0	4	6	23.87	<0.05
>10 years	2	0	0	1	4	7		
Total	12	1	2	1	14	30		

Discussion

Immune dysfunction in BD and schizophrenia triggers higher morbidity and mortality rates than in the general population. There is heightened urgency for their prevention and early correction (Sfera *et al.*, 2017). Therefore, until this need is met, optimal utilization of available pharmacological and nonpharmacological tools is crucial for the overall well-being of these patients.

To allow better diagnostic procedures and therapeutic strategies in schizophrenia and bipolar patients, use of easy accessible biomarkers has been recently suggested (Lai *et al*., 2016; Perkovic *et al*., 2017; Stahl, 2017).

The term 'Theranostic biomarkers' was introduced which refers to novel tests, indicators, or biomarkers used to identify the individual patient who will benefit from the most appropriate, efficacious treatment, given in the optimal dose, without toxic side effects and predict treatment response (Perkovic *et al*., 2017). It is an answer to the unmet needs in medicine and especially in psychiatry to achieve personalized medicine approach in treatment; to improve diagnoses and to combine diagnostic processes with the best possible therapeutic strategies (Lai *et al*., 2016).

Personalized medicine, now generally referred to as 'precision medicine,' can be described as providing the right patient with the right treatment at the right dose at the right time, and it has become a promising and controversial issue in healthcare research in recent years (Fraguas *et al*., 2017). Consequently, the use of new statistical techniques that make it possible to describe patient populations as a whole and patients as individuals is necessary. Unfortunately, these recommendations have still not been incorporated into most evidence-based studies (Schork, 2015).

Accordingly, the objective of this study was to evaluate and assess IL1B and IL6 as a marker for immune dysfunction in patients with BD and schizophrenia and to compare them to apparently healthy control group.

This study is a cross-sectional comparative study; the sample of patients was recruited from patients, already diagnosed as BD and schizophrenia, attending thepsychiatric outpatient clinic at Al-Zahraa University Hospital for follow up, while the control sample was recruited from apparently healthy medical and paramedical staff, working at Al-Zahraa University Hospital.

Discussion of sociodemographic characteristics

In this study, the majority of patients in the bipolar group and schizophrenia group are in the range of 20–29 years and this is in line with recent studies that BD starts during youth, with onset in the range of 18–22 years, and then persists across the life span (Strakowski *et al*., 2014). Similarly, it was proved that the typical age of onset for schizophrenia is in late adolescence or early 20s with a slightly later onset in women (Gogtay *et al*., 2013).

Available studies had proved that men and women are equally likely to develop BD (Gara *et al*., 2012) and that the incidence and prevalence of schizophrenia shows that men are more likely to develop schizophrenia than women (1.4 : 1) (Nonaka *et al*., 2013). However, other studies found that there were no gender differences between both sexes in the prevalence of schizophrenia in the general population (Ochoa *et al*., 2012). In the current study women represent the majority of patients in the bipolar group; this difference may be due to the high follow-up rate of female patients to outpatient clinics of Al-Zahraa University Hospital. On the other hand, the majority of patients in the schizophrenia group are men and this is in line with studies suggesting that.

Discussion of the descriptive study

Inflammation is a complex biological response to harmful stimuli and it is mediated by cytokine cascades, cellular immune responses, oxidative factors, and hormone regulation (Kunz *et al*., 2011). Cytokines, in particular, are supposed to play a critical role in infectious and inflammatory processes, mediating the crosstalk between the brain and the immune system (Anderson *et al*., 2013).

From this perspective, it seems that both schizophrenia and BD are associated with an imbalance in inflammatory cytokines? in fact, some of these could represent biological markers of illness and could be possible targets for pharmacological treatments (Altamura *et al*., 2014).

In the current study, it was found that the mean of serum IL1B level was higher in the bipolar group than the control group with a statistically significant difference. This result is consistent with other studies by Barbosa *et al*. (2014). However, Munkholm *et al*. (2013) in their meta-analysis study found no significant relation for IL1β level between the bipolar group and healthy controls. This discrepancy may be due to the small sample sizes and a lack of control for confounding factors in individual studies.

In the bipolar group, it was also found that the mean serum for IL1B level is higher than that of the schizophrenia group; however, there is no statistically significant difference. This may indicate that IL1B is a trait marker for BD (Maletic and Raison, 2014). These results together with the result found in our study may support the notion of altered proinflammatory cytokine levels in bipolar and the possible role of IL1B in the pathophysiology of BD (Muneer, 2007).

Considering serum IL1B in the schizophrenia group, it is higher than that of the control group; however, there is no statistically significant difference between both groups. This result is consistent with that of the study done by Shibuya *et al*. (2013). However, this finding is not consistent with that of the study conducted by Capuzzi *et al*. (2017), which aimed at measuring the cytokine levels after antipsychotic treatment in drug-naïve participants with first-episode psychosis where they found a significant decrease in IL1B level after 4 weeks of antipsychotic treatment. This discrepancy may be due to the different inclusion and exclusion criteria between our study and the latter study.

Several studies have reported that IL6 plays a crucial role in schizophrenia and BD to determine biological changes observed during the course of illness (Frydecka *et al*., 2014).

Studies by Abdel Samie *et al*. (2015); Goldsmith *et al*. (2016); Ghosh (2017) have found that there was an increase in serum level of IL6 in schizophrenia and bipolar groups.

In this study, it was also found that IL6 level was higher in the bipolar group and the schizophrenia group than that of the control group with a high statistically significant difference. Interestingly, the similarities (i.e. serum increase of IL6 concentrations) between schizophrenia and BD support a 'continuum' between the two disorders and that cytokine dysregulation could be responsible for the neurodegenerative aspects observed in both schizophrenia and BD (Altamura *et al*., 2014).

However, the finding of increased serum IL6 in this study was in contrast with the results of Hatata and Attlah (2009), which aimed at characterizing the immunological variations of Egyptian patients with BD and schizophrenia by the quantification of the serum levels of IL6. They reported that BD patients showed a statistically significant increase in IL6 when compared with controls while no statistically significant difference in the mean level of serum IL6 was found between patients with schizophrenia and healthy controls though it was still relatively higher in the schizophrenia group. This discrepancy between the current result and the result of Hatata and Attlah (2009) may be due to the small control group in the latter study. Moreover, in the latter study, obese participants were not excluded, which might have acted as a confounding factor because of obesity on IL6 level.

As regards the psychometric tools conducted in this study, the mean for YMRS in the bipolar group was 15.7, indicating manic features. On the other hand, the mean of PANSS, applied to the schizophrenia group, positive subscores was 27.17 which is equivalent to moderate degree of positive symptoms, and the mean of PANSS negative subscore was 23.07, which is equivalent to a mild degree of negative symptoms. Several studies have reported that bipolar I is more prevalent than bipolar II (Merikangas *et al*., 2011; Barbosa *et al*., 2014). This is inconsistent with the distribution of the type of BD in the bipolar group of the current study, where bipolar type I represents the majority of cases with a percentage of 83.3%.

Discussion of the analytical study

As regards the correlation of age at onset of illness and its effect on biological markers, the following results had been found; in the schizophrenia group, IL6 showed high significance and positive correlation with the age at onset of illness. This result was in agreement with the finding of the study conducted by Dunjic *et al*. (2013); Bai *et al*., (2014); however, this finding was not in line with the result of Abdel Samie *et al*. (2015), this may be attributed to the fact that the patients with schizophrenia in the latter study were at least 4-week antipsychotic drug free before withdrawal of the serum samples, while in our study the patients were maintained on their medication which may have caused the difference in the mean serum IL6 levels in both studies.

This may explain that antipsychotics used by patients can cause a decrease in serum IL6 level and the time needed to return to its baseline value after stopping antipsychotic drugs is not clearly defined (Bai *et al*., 2014).

As regards the duration of illness and its correlation with biological inflammatory markers done in this study, the following results had been found in the schizophrenia group. It was found that IL6 showed a significance and positively correlated with the duration of illness, this finding was in agreement with the finding of the study conducted by Hatata and Attlah (2009). However, this finding was not in line with the result of Bai *et al*. (2014), the latter study aimed at measurement of serum IL6 in remission and exacerbation phases while in our study all stages of illness was studied.

In view of the bipolar group, IL1B shows a high significance to the duration of illness which is in agreement with the result of the study done by

Maletic and Raison (2014). This finding may indicate that IL1B is a trait marker for BD and that the differences in immune status may alter in different stages of illness. Moreover, they could be different in early onset and late onset (Altamura *et al*., 2014).

As regards the number of episodes of illness and the serum level of IL6, it was found that no significant correlation was found in the bipolar group. This result is consistent with the results of Zhang *et al*. (2002). and inconsistent with the result of Bai *et al*., 2014.

It is of value to add that observed difference with some of the previous research results may occur due to the different biological material that was analyzed (serum vs plasma vs CSF), different essay method, small sample size, various phases of disease (acute vs chronic, active phase vs remission) and confounding factors such as BMI, smoking, age, and sex. Furthermore, previous therapy was often not taken systematically into account (Söderlund *et al*., 2011).

It is of great value to say that with the introduction of immunological findings in schizophrenia and BD, it is becoming clear that the etiopathology of schizophrenia and BD is related to a range of interacting variables which include genetic, infectious, and immune factors which all function as major predisposing and triggering factors. These multiple factors, like pieces of a mosaic (genetic, infectious and immune), may interplay in different forms, leading to the expression of varying combinations and diverse phenotypic expression of diseases (Dickerson *et al*., 2017). After introducing this work, together with the various studies reported, it may be of value to say brain tissue is able to engender immune processes and be influenced by them.

Conclusion

There is mounting evidence of increased immune markers, particularly pro-inflammatory cytokines in the periphery of BD and schizophrenia and IL1B may be considered as a biological marker of BD. So increased awareness of factors such as inflammation and autoimmunity may facilitate new understanding of mental disorders and provide new insight into treatment-resistant patients. Also, identifying biomarkers could represent new tools which could help to improve diagnosis and find prognosis markers. This will offer great promises toward a better understanding of etio-pathological mechanisms involved in BD and schizophrenia, and for the development of prevention and personalized treatments.

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Nil.

Conflicts of interest
There are no conflicts of interest.

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