Relationship of serum interleukin-6 and cognitive functions in patients with schizophrenia, a case–control study

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Background
Interleukin-6 (IL-6) is assumed to play a role in the emergence of cognitive deficits in schizophrenia.

Aim
The aim of this work was to assess cognitive functions in the domains of working memory, executive functions, psychomotor speed, and sustained attention in patients with schizophrenia and to determine its relationship to serum levels of IL-6.

Methods
Forty patients with schizophrenia recruited from the Kasr Al-Ainy psychiatric outpatient clinic and forty healthy controls matched in age, sex, and educational level to the patients' group were assessed and compared as regards the level of serum IL-6. Cognitive functions were assessed using letter cancellation test, digit symbol coding test, digit span, visual memory span, and Wisconsin card sorting test.

Results
The mean level of serum IL-6 of the patients with schizophrenia was significantly higher than that of the control group. Patients showed poorer performance in all cognitive tests. There was a statistically significant negative correlation between the level of serum IL-6 and visual memory span backward score.

Conclusion
Patients with schizophrenia have higher levels of serum IL-6. They show poorer cognitive performance in the domains of sustained attention, verbal and visual working memory, processing speed and executive functions, and visual memory deficits. There is a correlation between serum IL-6 and visual memory deficits in patients with schizophrenia.

Keywords:
cognitive functions, schizophrenia, serum interleukin-6

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Introduction

Cognitive symptoms of schizophrenia typically involve disturbances in executive functions, working memory impairment, and inability to sustain attention [1]. Evidence for the involvement of the immune system in schizophrenia has accumulated. Schizophrenia has been associated with decreased mitogen-induced lymphocyte proliferation, increased numbers of total T and T-helper cell [2] and the presence of numerous peripheral pro-inflammatory cytokines such as interleukin (IL)-1β,interleukin (IL) 6 and IL-8 [3].

Cytokines are proteins that modulate systemic and central nervous system responses to infection, inflammation, and injury [2]. Cytokines such as IL-2, tumor necrosis factor-α, and interferon γ are produced by T-helper 1 (Th1) cells, whereas IL-4, IL-6, and IL-10 are produced mainly by T-helper 2 (Th2) cells. Circulating levels of IL-6 were found to be higher in patients with schizophrenia. The 'Th2 hypothesis' suggests that the Th1–Th2 balance is shifted to Th2 in schizophrenia. Increased IL-6 activity in schizophrenia is considered to be evidence supporting the Th2 hypothesis [4].

Changes in cytokines and cytokine receptors have been reported in plasma, serum, and cerebrospinal fluid of schizophrenic patients, particularly an increase in serum IL-6 [4,5]. The mechanisms through which inflammatory cytokines such as IL-6 mediate the onset of schizophrenia are still largely under investigation and may include interaction with multiple pathways such as monoamine metabolism, neuroendocrine function, and synaptic plasticity [6]. Besides schizophrenia, IL-6 serum levels were also found to be elevated in other psychiatric disorders such as depression [7] and Alzheimer's disease [8].

There is a positive correlation between the severity of cognitive deficits and enhanced levels of inflammatory markers in schizophrenic patients, including IL-1β, IL-6, tumor necrosis factor-α, C-reactive protein, and S100B [1]. However, cognition is sparsely addressed in studies

investigating immune and inflammatory aspects of schizophrenia [9]. Serum IL-6 level was also found to be elevated transiently after electroconvulsive therapy [10], in medical conditions such as obesity [11], diabetes [12], systemic lupus erythematosus [13], rheumatoid arthritis [14], and both acute [15] and chronic liver diseases [16].

As regards the impact of antipsychotic intake on levels of IL-6, inconsistent results have been observed even when specific antipsychotics were investigated separately [4]. Interestingly, growing evidence from clinical studies with nonsteroidal anti-inflammatory agents points to the favorable effects of immunomodulatory therapy in schizophrenia and in particular in attenuating the cognitive impairment in these patients [9].

This study was based on the hypothesis that serum IL-6 level is higher in patients with schizophrenia than in healthy controls, which may reflect a possible immune pathophysiology in these patients. Patients with schizophrenia were expected to perform worse than healthy controls in the cognitive domains of sustained attention, working memory, processing speed, and psychomotor speed, as well as in executive functions, and it was hypothesized that there is a relationship between serum IL-6 level and cognitive deficits in these patients.

The aim of the study was to assess cognitive functions in the domains of working memory, executive functions, psychomotor speed, and sustained attention in patients with schizophrenia and to determine its relationship to serum levels of IL-6 in these patients.

Patients and methods

Design

The study was a cross-sectional comparative study, and the sample included was a convenient one.

Participants

Participants included in this study were 40 patients with schizophrenia with active symptoms diagnosed according to the *Diagnostic and Statistical Manual of Mental Disorders*, 4th ed., text revision (DSM-IV-TR) criteria recruited from the Kasr Al-Ainy psychiatric outpatient clinic, as well as 40 healthy controls matched in age, gender, and educational levels to the patients' group. The controls were volunteers working in Kasr Al-Ainy and their relatives. The recruitment of the participants started in October 2012 and ended in April 2014. It was difficult for some patients to continue the lengthy psychometric assessment, and this led to the dropout of seven patients who were replaced by others.

Patients were selected on the basis of the inclusion criteria of being in the age range of 20–50 years to minimize the confounding effect of aging on cognitive functions, being literate, and nonadherent on psychotropic drugs for at least 2 weeks before the day of assessment (not stopped by the researchers) to reduce their possible confounding effect on cognitive performance and serum level of IL-6. Patients with other psychiatric comorbidities including substance abuse, clinically subnormal mentality, and those with electroconvulsive therapy administration in the past 6 months were excluded.

The exclusion criteria for both patients and controls were having a medical or neurological condition, acute allergies or infections, and intake of antibiotics, anti-inflammatory, or immunomodulatory drugs at the time of assessment. History of significant head trauma was also an exclusion criterion to avoid its possible confounding effect on cognitive functioning. Participants with BMI more than or equal to 30 were also excluded because of confounding effect of obesity on serum level of IL-6. In the control group, in addition to the above-mentioned exclusion criteria, participants with past or family history of psychiatric disorders were excluded to minimize the possible confounding effects on cognitive performance.

Methods

Procedure

The diagnosis of schizophrenia according to DSM-IV criteria and the exclusion of psychiatric comorbities in patients were confirmed by the Structured Clinical Interview for DSM-IV Disorders [17] that was translated to Arabic by Hatata [18], and the clinical information was recorded during the interview. The control group was screened through the screening questions of the Structured Clinical Interview for DSM-IV Disorders interview to exclude participants with current or past history of psychiatric disorders including substance abuse.

Both cases and controls were subjected to the following:

(1) Clinical and laboratory assessments
   (a) The exclusion of medical conditions and infections was ensured by history taking, physical examination, and laboratory tests (complete blood count, liver and kidney function tests, random blood sugar, and erythrocyte sedimentation rate).
   (b) Venous samples were collected by a nurse from all participants by aseptic venipuncture, and the blood was then added to serum separator vacutainer tubes and centrifuged at a rate of 3000 rpm by a trained laboratory technician. The separated serum was harvested and frozen until assay at −20°C. Serum IL-6 was assayed in one setting using 'IL-6 enzyme linked immunosorbent technique assay kit' (AviBion Human IL-6 ELISA; Orgenium Laboratories, Viikinkaari 6, Helsinki, Finland).
   (c) The procedure performed was as follows: first 50 µl of standard starting sample, as well as the test sample, and sample diluents were added as a blank into the appropriate wells of the strips. Then 50 µl of green-colored biotin antibody was promptly added to each well. After incubation, they were then washed with wash buffer and 100 µl of peroxidase-labeled streptavidin solution was added. Then 50 µl of tetramethylbenzidine one-step substrate reagent was added to each well and

incubated for 20 min at room temperature. Next, 25 µl of stop solution (H_2SO_4) was added to each well and then read at 450 nm against 630 nm immediately.

(2) Psychometric assessment
   (a) Letter cancellation test by Diller *et al.* [19] in its Arabic version standardized by El Kholi [20] was used to assess sustained attention [21]. The participants were asked to cancel two fixed Arabic letters as fast as they could, and the time taken in seconds was calculated. Omission errors were also counted.
   (b) The digit symbol coding subtest of the Arabic version of the Wechsler adult intelligence scale translated by Melika and Ismail [22] was used to assess psychomotor speed [23] and mental processing speed [24]. In this test, participants were asked to transcribe a digit symbol code as quickly as possible with a time limit of 90 s.
   (c) The digit span subtest of the Arabic version of the Wechsler adult intelligence scale translated by Melika and Ismail [22] was used to assess verbal working memory [24]. The participant was asked to repeat a dictated series of digits forward and another backward with two trials each time. The score of the digit forward span and digit backward span was recorded for each participant.
   (d) The visual memory span of the Wechsler memory scale by Wechsler [25] was used to assess visual working memory [26]. In this test, the examiner touched a sequence of colored squares that the participant was asked to touch in the same order. In the second task, the participant was asked to touch the squares touched by the examiner but in the reverse order.
   (e) The Wisconsin card sorting test (WCST) by Heaton *et al.* [27] in its computer administered version to assess executive functions. The test consists of four stimulus cards that were presented on the computer screen in front of the subject. Response cards, which had designs similar to those on the stimulus cards, varying in color, geometric form, and number, appeared on the screen in front of the subject, one at a time. The subject was then asked to match each of the cards to one of the four stimulus cards and was given feedback each time whether he or she was right or wrong.

Statistical analysis

Precoded data were entered into the statistical package of the social science software program (IBM SPSS for Windows, version 21.0; IBM Corp., Armonk, New York, USA) [28] to be statistically analyzed. Data were summarized using mean and SD for quantitative variables and frequency and percentage for qualitative ones. Comparison between groups was performed using independent sample *t*-test (if parametric) or Mann–Whitney *U*-test (if nonparametric). Spearman's correlation coefficients were calculated to signify the association between different quantitative variables. *P* values less than 0.05 were considered statistically significant, and *P* values less than 0.01 were considered highly significant.

Ethical consideration

The research was approved by Ethical and Research Committee, Faculty of Medicine, Cairo University. An informed written consent was obtained from both patients and controls before participating in the study. The consent form included details about the study, as well as the participant's right to withdraw from the study at any time.

Results

The mean age of the patients was 31.9±8.1 years and that of the healthy control group was 31.2±7.4 years. The mean age at illness onset of the schizophrenic group was 23 years and the mean duration of illness was 9.0±7.8 years.

The mean serum IL-6 level (35.3±10.1) in the schizophrenic group was higher than the mean serum IL-6

Table 1 Comparison between the schizophrenia group and the healthy control group regarding the scores of the cognitive tests

Cognitive tests	Schizophrenia group (mean±SD)	Healthy control group (mean±SD)	*P*-value
Letter cancellation test			
Omission errors	6.4±9.5	2.3±2.4	0.01
Time per second	164.3±58.5	90.0±22.0	<0.001
Digit symbol coding	19.3±6.4	46.7±9.7	<0.001
Digit span test			
Forward	4.7±0.9	6.2±1.4	<0.001
Backward	2.8±1.6	4.7±1.3	<0.001
Visual memory span test			
Forward	5.0±1.3	8.5±2.2	<0.001
Backward	3.7±1.4	7.3±1.7	<0.001
WCST			
Total errors	82.2±14.7	34.7±13.4	<0.001
Categories completed	0.4±0.8	5.7±2.6	<0.001
Perseverative errors	22.2±26.1	20.1±10.0	0.6
Nonperseverative errors	60.0±31.7	14.6±9.2	<0.001

Mann–Whitney *U*-test.
WCST, Wisconsin card sorting test.

Table 2 Correlation between the serum interleukin-6 level and each of the cognitive tests scores in the schizophrenia group

	Serum interlekin-6	*r*	*P*-value
Letter cancellation test	Omission errors	0.058	0.483
	Time per second	−0.001	0.994
Digit span test	Digit symbol coding	−0.081	0.619
	Forward	0.098	0.549
	Backward	−0.200	0.217
Visual memory span test	Forward	0.034	0.837
	Backward	−0.329	0.038
WCST	Total errors	0.293	0.066
	Categories completed	0.028	0.863
	Perseverative errors	−0.039	0.810
	Nonperseverative errors	0.137	0.401

r = Spearman's correlation coefficient.
WCST, Wisconsin card sorting test.

level in the healthy control group (27.5 ± 7.9), with a statistically significant difference ($P < 0.001$).

Table 1 shows that the mean omission errors score and mean time/s score in the letter cancellation test were higher in schizophrenia patients than in controls, and the mean score of the digit symbol coding test, the digit span forward and backward tests, and the visual memory span forward and backward tests were lower in patients than in controls, with a statistically significant difference between both groups.

As regards the performance on the Wisconsin card sorting test, patients showed a higher mean number of total errors, perseverative errors, and nonperseverative errors, as well as a lower mean number of categories completed than controls, which revealed a poorer performance of patients in this test than in the control group, all with statistically significant differences except the mean number of perseverative errors, where the patients also showed a larger mean than controls but the difference between both groups was not statistically significant.

Table 2 shows that there was a statistically significant negative correlation between the visual memory span backward score and the serum IL-6 level in the schizophrenia group; however, there were no statistically significant correlations between serum IL-6 level and the other cognitive test scores.

Discussion

Cognitive functioning is moderately to severely impaired in most important domains including attention, memory, processing speed, and executive functions in schizophrenia patients [9]. The aim of the study was to assess cognitive functions in the domains of working memory, executive functions, psychomotor speed, and sustained attention in patients with schizophrenia and to determine its relationship to serum levels of IL-6.

In the patients' group, the mean serum IL-6 level was higher than that of the control group, with a statistically significant difference, which was consistent with the results of the studies by Miller *et al.* [29], Frydecka *et al.* [9], and Shahraki *et al.* [30] that support the notion of altered proinflammatory cytokine levels in schizophrenia and the possible role of IL-6 in the pathophysiology of schizophrenia. A study conducted by Hatata and Attlah [31], which aimed at characterizing the immunological variations of Egyptian patients with bipolar disorder and schizophrenia by the quantification of the serum levels of IL-6, also showed a relatively higher level in the schizophrenia group than in the healthy control group, but unlike our study the difference was not statistically significant. This discrepancy may be due to the small control group in the latter study or because of the difference in sample selection, where all the patients in the latter study were newly admitted with active psychotic symptoms.

In the present study, the patients with schizophrenia showed poorer performance than controls in the cognitive tests applied to assess sustained attention (letter cancellation test), processing and psychomotor speed (digit symbol coding), verbal and visual working memory (digit span and visual memory span, respectively), and executive functions (WSCT), with a statistically significant difference between the mean scores of almost all the cognitive tests. This is concordant with the results of the meta-analysis conducted by Fioravanti *et al.* [32], where patients with schizophrenia showed a statistically significant poorer performance than controls on tests applied to assess working memory, attention, and executive functions.

This is also consistent with the results of a case–control study conducted by Frydecka *et al.* [9], in which the patients with schizophrenia performed worse than the healthy control group with a statistically significant difference in the digit symbol coding and the digit span subscores of the Wechsler adult intelligence scale (for assessment of processing speed and verbal working memory respectively) and also in the trail-making test part A for assessment of attention.

However, in our study, the WSCT perseverative errors subscore was higher in patients than in controls, but the difference was statistically insignificant unlike the mean of nonperseverative errors subscore, which was higher with a statistically significant difference in the patients' group. This finding was concordant to that of the comparative study conducted by Garas [33], which studied the executive functioning in an Egyptian sample of patients with schizophrenia in comparison with healthy controls and patients with bipolar disorder. In both studies, the statistically insignificant difference in this domain may be because of the relatively small sample size.

However, this finding was inconsistent with that of the study conducted by Wobrock *et al.* [34], which showed that the patients with schizophrenia had statistically significantly higher WSCT perseverative errors mean score than healthy controls. This discrepancy may be attributed to the relatively small sample size in that study (24 patients and 23 controls) or to the possibility of psychotropic drug intake as the medication status was not clearly mentioned. Psychotropics intake may affect cognitive performance as a direct consequence of the

mechanism of action of the psychotropic agent, or indirectly through side effects such as sedation [33].

The correlations conducted in this study revealed a statistically significant negative correlation between the serum IL-6 level and the visual memory span backward score for assessment of working memory (i.e. higher IL-6 levels were associated with poorer performance in this test), which is consistent with the finding of the case–control study conducted by Frydecka *et al.* [9], in which serum IL-6 level showed a statistically significant correlation with the trail-making test, part B score, used to assess both working memory and executive control. This association between IL-6 and working memory further supports the extensive evidence suggesting that IL-6 may influence cognitive functioning [9]. However, inconsistent with our results, the latter study found a statistically significant negative correlation between serum IL-6 level and both the digit symbol coding and the digit span forward score. The discrepancy in these findings may be due to the smaller sample size in our study.

The latter study also found a statistically significant positive correlation between the serum IL-6 level and the trail-making test, part B score, implicating the association of serum IL-6 level with poorer executive control [9], which was not concordant with our study, in which no significant correlation was found between serum IL-6 level and any of the WSCT test scores. In addition, the same study showed a positive correlation between serum IL-6 level and the score of the trail-making test part A, used to assess attention, unlike our study, where no significant correlation was found between serum IL-6 level and the score of the letter cancellation test. This discrepancy may be because of the different psychometric tools applied to assess executive function and attention in both studies, or because of the different number of participants or both.

One of the limitations in this study is the relatively small sample size, although it is comparable to multiple studies aiming at assessment of differences between patients with schizophrenia and controls regarding serum IL-6 levels. The sample was a convenient sample, which is another limitation. Not all cognitive domains were assessed; however, those assessed in this study were the most commonly affected in schizophrenia.

Conclusion

Patients with schizophrenia have a higher level of serum IL-6 than healthy controls. They show poorer cognitive performance in the domains of sustained attention, verbal and visual working memory, processing speed, and executive functions. There is a significant negative correlation between serum IL-6 level and visual memory span backward score (which reflects visual working memory performance) in patients with schizophrenia.

Recommendations

Longitudinal studies with larger sample sizes and studies assessing at-risk individuals may help in better understanding of the possible neuroinflammatory pathophysiology in schizophrenia and the potential role of IL-6 as a biomarker. In addition, similar studies assessing the relation between serum IL-6 levels and the various cognitive deficits in patients with schizophrenia, including deficits in social cognition, can help elucidate the possible relation between cognition in schizophrenia and immunological dysregulation. It is also highly recommended to conduct clinical trials assessing the role of anti-inflammatory treatment in amelioration of the cognitive symptoms of schizophrenia. Given the various cognitive deficits in patients with schizophrenia, implementation of cognitive remediation programs may help improve their cognitive performance and subsequently their quality of life as a whole.

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Conflicts of interest

There are no conflicts of interest.

References

1 Meyer U, Schwarz M, Müller N. Inflammatory processes in schizophrenia: a promising neuroimmunological target for the treatment of negative/cognitive symptoms and beyond. Pharmacol Ther 2011; 132:96–110.

2 Scmitt A, Bertsch T, Tost H, Bergmann A, Henning U, Klimke A, Falkai P. Increases serum interleukin-1B and interleukin-6 in elderly, chronic schizophrenic patients on stable antipsychotic medication. Neuropsychiatric disease and treatment 2005; 1:171.

3 Drexhage RC, Hoogenboezem TA, Cohen D, Versnel MA, Nolen WA, van Beveren NJ, Drexhage HA. An activated set point of T-cell and monocyte inflammatory networks in recent-onset schizophrenia patients involves both pro and anti-inflammatory forces. Int J Neuropsychopharmacol 2011; 14:746–755.

4 Lin C-C, Chang C-M, Chang P-Y, Huang T-L. Increased interleukin-6 level in Taiwanese schizophrenic patients. Chang Gung Med Journal 2011; 34:375–381.

5 Kunz M, Cereser KM, Goi PD, Fries GR, Teixeira AL, Fernandes BS, *et al.* Serum levels of IL-6, IL-10 and TNF-α in patients with bipolar disorder and schizophrenia: differences in pro- and anti-inflammatory balance. Rev Bras Psiquiatr 2011; 33:268–2274.

6 Mondelli V, Dazzan P, Pariante CM. Immune abnormalities across psychiatric disorders: clinical relevance. B J Psych Advances 2015; 21:150–156.

7 Dowlati Y, Herrmann N, Swardfager W, Liu H, Sham L, Reim EK, Lanctôt KL. A meta-analysis of cytokines in major depression. Biol Psychiatry 2010; 67:446–457.

8 Swardfager W, Lanctôt K, Rothenburg L, Wong A, Cappell J, Herrmann N. A meta-analysis of cytokines in Alzheimer's disease. Biol Psychiatry 2010; 68:930–941.

9 Frydecka D, Zej Misiak B, Pawlak-Adamska E, Karabon L, Tomkiewicz A, Sedlaczek P, *et al.* Interleukin-6: the missing element of the neurocognitive deterioration in schizophrenia? The focus on genetic underpinnings, cognitive impairment and clinical manifestation. Eur Arch Psychiatry Clin Neurosci 2015; 265:449–459.

10 Lehtima K, Kera T, Huuhka M, Palmio J, Hurme M, Leinonen E, Peltola J. Increase in plasma proinflammatory cytokines after electroconvulsive therapy in patients with depressive disorder. J ECT 2008; 24:1.

11 Kern P, Ranganathan S, Li C, Wood L, Ranganathan G. Adipose tissue tumor necrosis factor and interleukin-6 expression in human obesity and insulin resistance. Am J Physiol Endocrinol Metab 2001; 280:E745–E751.

12 Kristiansen O, Mandrup-Poulsen T. Interleukin-6 and diabetes: the good, the bad, or the indifferent? Diabetes 2005; 54:S114–S124.

13 Tackey E, Lipsky PE, Illei GG. Rationale for interleukin-6 blockade in systemic lupus erythematosus. Lupus 2004; 13:339–343.

14 Nishimoto N. Interleukin-6 in rheumatoid arthritis. Curr Opin Rheumatol 2006; 18:277–281.

15 Sun Y, Tokushige K, Isono E, Yamauchi K, Obata H. Elevated serum interleukin-6 levels in patients with acute hepatitis. J Clin Immunol 1992; 12:197–200.

16 Tilg H, Wilmer A, Vogel W, Herold M, Nölchen B, Judmaier G, Huber C. Serum levels of cytokines in chronic liver diseases. Gastroenterology 1992; 103:264.

17 First M, Spitzer R, Williams G, Williams J. Structured and clinical interview for DSM IV. Washington DC, American Psychiatric Press; 1996.

18 Hatata H. Dual diagnosis in substance abuse a study in an egyptian sample, MD Thesis, Ain Shams University. 2004.

19 Diller L, Ben-Yishay Y, Gerstman L, Goodkin R, Gordon W, Weinberg J. Studies in cognition and rehabilitation in hemiplegia (Rehabilitation Monograph No 50). New York, NY: New York University Medical Center Institute of Rehabilitation Medicine; 1974.

20 El-Kholi SW. Attention in psychiatric patients. A psychometric study, MA, Thesis, Faculty of Arts University. 1985.

21 Ronald T, Patricia C, Richard L. Neurocognitive functioning and magnetic resonance imaging in children with sickle cell disease. J Pediatr Psychol 2000; 25:503–513.

22 Melika L, Ismail M. Wechsler adult intelligence scale. El Nahda Elmasriya 1996.

23 Gunstad J, Benitez A, Hoth K, Spitznagel MB, McCaffery J, McGeary J, *et al*. P-selectin 1087G/A polymorphism is associated with neuropsychological test performance in older adults with cardiovascular disease. Stroke 2009; 40:2969–2972.

24 Doyle A, Wilens T, Kwon A, Seidman LJ, Faraone SV, Fried R, *et al*. Neuropsychological functioning in youth with bipolar disorder. Biol Psychiatry 2005; 58:540–548.

25 Wechsler D. *Manual for the Wechsler Memory Scale-Revised*. San Antonio, TX: Psychological Corporation; 1987.

26 Kindermann F, Mehnert A, Scherwath A, Schirmer L, Schleimer B, Zander A, Koch U. Cognitive function in the acute course of allogeneic hematopoietic stem cell transplantation for hematological malignancies. Bone Marrow Transplatation 2007; 39:789–799.

27 Heaton R, Chelune G, Talley J, Kay G, Curtiss G. Wisconsin card sort test manual: revised and expanded. Odessa, FL: Psychological Assessment Resources; 1993.

28 IBM Corp. *IBM SPSS statistics for Windows, version 210*. Armonk, NY: IBM Corp; 2013.

29 Miller BJ, Buckley P, Seabolt W, Mellor A, Kirkpatrick B. Meta-analysis of cytokine alterations in schizophrenia: clinical status and antipsychotic effects. Biol Psychiatry 2011; 70:663–671.

30 Shahraki A, Sarabandi R, Kianpur M, Zakeri Z. Elevated serum interleukin-23 and interleukin-6 levels in schizophrenic patients compared to those in healthy controls. Shiraz E Med J 2016; 17:6.

31 Hatata H, Attlah MF. The serum level of tumor necrosis factor alpha and interleukin-6 in bipolar affective disorder and schizophrenia (study in Egyptian sample). Curr Psychiatry 2009; 16:116–126.

32 Fioravanti M, Bianchi V, Cinti MA. Cognitive deficits in schizophrenia: an updated metanalysis of the scientific evidence. BMC Psychiatry 2012. 22–34.

33 Garas OF. Executive dysfunction in patients with schizophrenia and bipolar disorder: a comparative study. Thesis submitted in partial fulfillment for MSc degree in psychiatry. Faculty of Medicine, Cairo University. 2014.

34 Wobrock T, Ecker U, Scherk H, Schneider-Axmann T, Falkai P, Gruber O. Cognitive impairment of executive function as a core symptom of schizophrenia. World J Biol Psychiatry 2009; 10:442–451.