ORIGINAL ARTICLE

The level of tumour necrosis factor-alpha and its relationship to the cognitive function of Malayan-Mongoloid patients with schizophrenia

Mustafa M. Amin[1], Abdul Rasyid[2], Elmeida Effendy[1], Nurmiati Amir[3], Dwi Anita Suryandari[4]

[1]Department of Psychiatry, [2]Department of Radiology; Faculty of Medicine, Universitas Sumatera Utara, Medan, [3]Department of Psychiatry, [4] Department of Biology; Faculty of Medicine, University of Indonesia, Jakarta; Indonesia

ABSTRACT

Aim Schizophrenia is a mental disorder and one of the suspected causes is cytokines. One of them is tumour necrosis factor-alpha (TNF-α). Cytokines have the potential to affect cognitive function. The study aimed to find a correlation of TNF-α level with the Mini-Mental State Examination (MMSE) score in patients with schizophrenia (PwS), and comparing the level of TNF-α levels between PwS and healthy controls.

Methods We conducted a cross-sectional analytic study and the study designs were correlation and comparative analysis, i.e. using a Mann-Whitney U test. A total number of 100 subjects were collected, and they were divided into two groups of PwS and control group, respectively.

Results The results found that most of the PwS subjects were 39 men (78.0%), while the control group were 28 men (56.%). The differences in TNF-α levels between PwS and control groups were found to be significant $p < 0.001$, there was no significant correlation between TNF-α level and the score of MMSE of the PwS with $p = 0.938$, with a very weak correlation that was $r = -0.011$, and a negative correlation direction.

Conclusion There was a significant difference between TNF-α level of PwS and control group, i.e. PwS group had lower TNF-α level compared to the control group. The TNF-α level of PwS group had a very weak effect on the cause of cognitive dysfunction in PwS group, yet the higher level of it could reduce MMSE score in PwS group.

Key words: cytokines, cognitive dysfunction, psychotic disorders

Corresponding author:
Mustafa M. Amin
Department of Psychiatry,
Faculty of Medicine,
Universitas Sumatera Utara
Jl. dr. T. Mansur No. 5, Medan, Indonesia
Phone: +62 81 2600 1772;
E-mail: mustafamamin78@gmail.com;
mustafa.mahmud@usu.ac.id
ORCID ID: http://orcid.org/0000-0003-0912-9372

Original submission:
28 November 2019;
Revised submission:
21 January 2020;
Accepted:
28 February 2020
doi: 10.17392/1108-20

Med Glas (Zenica) 2020; 17(2): 445-450

INTRODUCTION

Schizophrenia is a mental disorder that usually appears in late adolescence or early adulthood, which affects about 21 million people worldwide (1). Thus far, the aetiology of schizophrenia is unknown, but several hypotheses related to this have been stated: schizophrenia is a neurodevelopmental disease; it is a neurodegenerative disease; and it is a progressive neurodevelopmental disease (2).

Another important point is the implication of cytokines in the aetiology or pathology of schizophrenia (3). One of the cytokines that play an essential role for schizophrenia is tumour necrosis factor-alpha (TNF-α). TNF-α level also increased significantly in patients with schizophrenia (PwS) compared to healthy controls (4-7). Studies with the same results were reported by O'Brien, Scully, and Dinan (8), i.e. there were significant differences in TNF-α level in the schizophrenia group of 13.49 pg/ ml±0.42 and 6.79 pg/ml±0.42 in the control group. This result is supported by Czerski et al. (9) who found a significant difference in the frequency of TNF-α between PwS and control group, 87.9% and 82.9%; this frequency increased to 90.7% of those who had a history of schizophrenia in the first and second-degree relatives. Similar results have also been reported by Rosario García-Miss et al. (10) who found that there was a significant difference between PwS and control group regarding the TNF-α values of 10.63 ± 4.65 pg/mL and 6.74±4,00 pg/mL, TNF-α levels in PwS were higher than in the group.

Inflammation is thought to have a role in the pathophysiological process of schizophrenia, and currently, various studies are being conducted to find out the anti-inflammatory effect in PwS (11). A literature review from Baune et al. (12) concluded that TNF-α has a neuroprotective or neurodegenerative function. Therefore, it remains debatable whether TNF-α can maintain or decrease cognitive function. A study conducted by Xiu et al. (13) found that TNF-α could mediate cognitive severity towards PwS. Thus far, different results have been found in previous studies. Therefore, more research is needed to support the statement of cytokines, such as conducting a study of the TNF-α, which has a relation with schizophrenia.

Malayan-Mongoloid people are one of the races living in Medan, Indonesia. It consists of two sub-races, i.e. Proto Malayan and Deutro Malayan. Our study focused on the Proto Malayan type only.

The aim of this study was to investigate the effect of TNF-α on the cognitive function of patients of the Malayan-Mongoloid race with schizophrenia in North Sumatera, and it was the first study in North Sumatera which assessed this.

PATIENTS AND METHODS

Patients and study design

This cross-sectional analytical study was carried out at the Outpatient and Inpatient Installation of the North Sumatera Psychiatric Hospital (R. S. J. Provsu) Prof. M. Ildrem during the period of 3 months in 2019. This psychiatric hospital is a referral psychiatric hospital in North Sumatra Province, and had an inpatient capacity of 400 beds. Patients who came to this psychiatric hospital were almost entirely Malayan-Mongoloid Race. The target population was PwS that were the patients of the Outpatient and Inpatient Installation of North Sumatera Psychiatric Hospital. The patients included the PwS group, and the healthy control group that fulfilled the inclusion and exclusion criteria. Inclusion criteria of PwS were: schizophrenic patients diagnosed based on the 10th edition of the International Classification of Disease and Related Health Problems criteria (14), aged 15-40 years, Malayan-Mongoloid Race, cooperative and willing to be interviewed. Exclusion criteria were: having a history of previous psychiatric disorders, having a general medical condition that affected brain structure, and obesity (defined by body mass index - BMI of ≥ 30). The inclusion criteria for the control group were: age 15-40 years, Malayan-Mongoloid Race, cooperative and willing to be interviewed, and no family history of having a mental disorder. Exclusion criteria for the control group were: having a history of previous psychiatric disorders, having a general medical condition that affected brain structure, and obesity. We took the control group from the people who lived near the hospital.

The sample size calculation used the following formula:

$$n_1 = n_2 = 2\left(\frac{[Z_\alpha + Z_\beta]S}{\bar{x}_1 - \bar{x}_2}\right)^2$$

The sample size was based on the sample size table with alpha 5% two-sided beta hypothesis of 10%, in which the assumption of the standard

deviation ratio was 1, it was found that n1 = n2 = 21 subjects. In this study, 50 subjects were taken for each group.

Next, the subjects and their relatives were asked to read the letter of statement of the research and sign the consent form after an explanation about the participation in the study. The study was approved by the Health Research Ethical Committee of Faculty of Medicine, Universitas Sumatera Utara.

Methods

Blood plasma sampling was carried out as followed: blood was drawn with a sterile syringe (aseptic) from a vein in the area where the upper arm meets the forearm (median cubital vein) for 6 mL. The blood was then kept in a vacutainer containing ethylenediaminetetraacetic acid (EDTA) and stored at 4-8 ^{o}C until the serum and plasma were separated.

The enzyme-linked immunosorbent assays (ELISA) examination was then performed using the human Quantikine TNF-alpha kit (R&D systems, Minneapolis, MA, USA) and read the results using the Thermo-Fisher machine. The cognitive function of the PwS was measured using Mini-Mental State Examination (MMSE) rating scale (15) that had been validated in the Indonesian language by Geriatric Psychiatry Section of Indonesia Psychiatry Association (16); the total score was divided into normal (24-30), probable cognitive disorder (17-23), and definite cognitive disorder (0-16). The rating scale itself only took less than 10 minutes to complete, and was relatively easy to use.

Statistical analysis

Statistical analysis began by normalizing the data using Saphiro-Wilk normality test. We found that the result was abnormal data, and continued the analysis using Mann-Whitney U test to compare the difference between the TNF-α level of PwS and control, and the Spearman correlation test to find the relationship of TNF-α level with MMSE score in the PwS group.

RESULTS

Among 100 patients analysed (50 patients in each PwS and control group) the males predominated over female patients in both groups, 38 (76.0%) in PwS and 28 (56.05) in control group, with higher average age of 35.42±2.78 years in PwS group. Higher BMI, of 23.79±2.98, in the control group was found. The average MMSE score was 21.00±4.56 in PwS group (Table 1).

Table 1. Baseline characteristics of patients with schizophrenia (PwS) and controls

Variable	Group	
	PwS (n=50)	**Control** (n=50)
Gender (No, %)		
Male	38 (76.0)	28 (56.0)
Female	12 (24.0)	22 (44.0)
Age (average±SD) (years)	35.42±2.78	29.38±5.75
BMI (average±SD)	21.57±2.02	23.79±2.98
MMSE*	21.00±4.56	-

*Data was only for the patients with schizophrenia BMI, body mass index; MMSE, Mini-Mental State Examination

The TNF-α level for PwS was 3.24 (0.65-43.80) pg/dL, while for the control group it was 16.25 (4.80-56.10) pg/dL (p<0.001) (Table 2). The boxplot comparison of these two groups was shown in Figure 1. We found that the PwS group had the lowest TNF-α level i.e. 0.65 pg/dL, much less varied in the TNF-α level and lower median compared to the control group. The highest of the TNF-α level was found in the control group, i.e. 56.10 pg/dL.

Table 2. Comparative analysis of TNF-α level between patients with schizophrenia (PwS) and the control group

Variable	Group		p
	PwS (n=50)	**Control** (n=50)	
TNF-α level (mean) (pg/dL)	3.24 (0.65-43.80)	16.25 (4.80-56.10)	<0.001

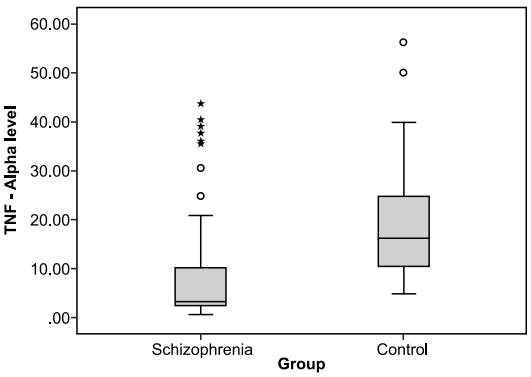

Figure 1. Boxplot graph results of comparison analysis of TNF-α level between patients with schizophrenia (PwS) and the control group

There was no significant correlation between TNF-α level and MMSE score (p=0.938); the correlation coefficient was very weak, and the direction was negative (r= -0.011). The higher TNF-α level resulted in lower MMSE score (Figure 2).

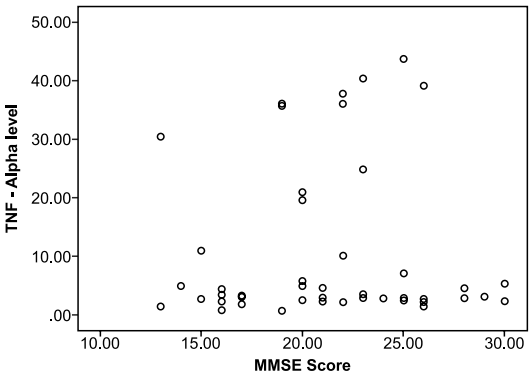

Figure 2. Scatter graph correlation analysis results between the TNF-α level and Mini-Mental State Examination (MMSE) score of patients with schizophrenia

DISCUSSION

The results in this study found predomination of male PwS patients, and it was the same as reported by Lv et al. (17), Garcia-Miss et al. (10), Kunz et al. (18), Tian et al. (19), Naudin et al. (4), and Kubistova et al. (20). Different results found that there were more females with schizophrenia than males as reported by Kowalski et al. (6), and Hope et al. (21). It was explained by the fact that males with schizophrenia were more frequently hospitalised compared to females, because males are less adherent to the treatment, and often commit suicide (22), or because females with schizophrenia were more responsive to the treatment and less than 50% experienced inpatient care (23).

In this study the mean of TNF-α level in the PwS group was lower compared to the control group. Similar results were reported by Chiang et al. (24) who found lower TNF-α in males. Other studies found the same results such as the study by Tian et al. (19), and Zhu et al. (25). We assumed that the similarities that we found were due to all of these studies conducted in Mongoloid race. Many studies showed different results, e. g. the TNF-α level in the PwS group was higher compared to the control group (4,26-30), and most of them were done in Caucasian race, except one study that was done in Indonesia.

Some conditions that potentially caused lower TNF-α level included antipsychotic drugs consumed by PwS (14,31), the chronicity of the schizophrenia (17), and variations in vitamin D levels in the body (32). Cytokines were thought to be involved in the regulation of several neurotransmitters, such as dopamine, serotonin, noradrenaline, and glutamate (33). A low level of inflammatory cytokines in the brain could still affect complex brain functions such as memory, mood, anxiety, cognition, and nerve activity (34,35). Cytokines, in this case, TNF-α had an essential role in regulating complexity including immunity and inflammation. Thus, the low TNF-α level in the PwS group indicated that there had been a defect during the induction of inflammatory pathways or active inhibition of these cytokines (17).

Our results show that there was no significant correlation between TNF-α level and MMSE score, and it had a very weak correlation coefficient. In schizophrenia, cognitive dysfunction happened before the appearance of positive and negative symptoms (12). The existence of TNF-α had an important role related to immunity and inflammation in the brain (36), and changes in the level of TNF-α start when the PwS is still in the mothers' womb (37). One mechanism that allows TNF-α to influence schizophrenia is through neuregulin-1. The neuregulin-1 gene along with the erb84 receptor acted for the occurrence of plasticity, myelination, and the formation of long-term potentiation, thus it had an important role in the cognitive function (12). The results of our study were supported by a study conducted by Hennessy et al. (38), which found that high TNF-α could induce a decrease of working memory. In addition, inhibition of TNF-α could also improve memory loss and spatial learning (39). The existence of TNF-α was also important in learning activities and memory because the presence of TNF-α could interfere with both processes. As stated before, inhibition of TNF-α could restore cognitive function (40). Some of the mechanisms offered related to the above statement are TNF-α having a contribution in astrogliosis, apoptosis, neurogenesis and permeability in the endothelial cell layer; thus, it can influence the cognitive function (41). This process started with prenatal inflammation resulting in abnormalities of cytokine levels including TNF-α resulting in neurodevelopment disorders. Specifically, concerning cognition, these effects included its relationship with the quality of life and overall function of PwS, which later influenced the outcome of the disease (42). This is supported by a literature review written by Misiak et al. (43), they also confirm that TNF-α has contributed to cognitive impairment in PwS.

In conclusion, no relationship between TNF-α and cognitive function of PwS was found. We thought that the age of the patients affected our results. Based on our findings of the coefficient correlation, the level of TNF-α may have a very weak effect on the cognitive function of PwS. It contradicts with previous studies that suggested that cytokines had an important role in influencing the cognitive function.

ACKNOWLEDGEMENTS

We want to thank all the patients and people who were willing to join our study, and the physicians and nurses at North Sumatera Psihiatric Hospital who had been cooperative with us, especially to Universitas Sumatera Utara for granting a fund for this study.

FUNDING

The study was funded by TALENTA funding of Universitas Sumatera Utara.

TRANSPARENCY DECLARATIONS

Competing interests: None to declare.

REFERENCES

1. World Health Organization. Schizophrenia. www.who.int/mental_health/management/schizophrenia/en (20 April 2018)
2. Gupta S, Kulhara P. What is schizophrenia: a neurodevelopmental or neurodegenerative disorder or a combination of both? A critical analysis. Indian J Psychiatry 2010; 52:21-7.
3. Nawa H, Takahashi M, Paterson PH. Cytokine and growth factor involvement in schizophrenia – support for the developmental model. Mol Psychiatry 2000; 5:594-603.
4. Naudin J, Capo C, Giusan B, Mège JL, Azorin JM. A differential role for interleukin-6 and tumor necrosis factor-α in schizophrenia? Schizophr Res 1997; 26:227-33.
5. Erbagci AB, Herken H, Köyloüglu O, Yilmaz N, Tarakçioglu M. Serum IL-1β, sIL-2R, IL-6, IL-8 and TNF-α in schizophrenic patients, relation with symptomatology and responsiveness to risperidone treatment. Mediators Inflamm 2001; 10:109-15.
6. Kowalski J, Blada P, Kucia K, Madej A, Herman ZS. Neuroleptics normalize increased release of interleukin-1β and tumor necrosis factor-α from monocytes in schizophrenia. Schizophr Res 2001; 50:169-75.
7. Theodoropoulou S, Spanakos G, Baxevanis CN, Economou M, Gritzapis AD, Papamichail MP, Stefanis CN. Cytokine serum levels, autologous mixed lymphocyte reaction and surface marker analysis in never medicated and chronically medicated schizophrenic patients. Schizophr Res 2001; 47:13-25.
8. O'Brien SM, Scully P Dinan TG. Increased tumor necrosis factor-alpha concentrations in excacerbations of schizophrenia. Psychiatry Res 2008; 160:256-62.
9. Czerski PM, Rybakowski F, Kapelski P, Rybakowski JK, Dmitrzak-Węglarz M, Leszczyńska-Rodziewicz A, Slopien A, Skibinska M, Kaczmarkiewicz-Fass M, Hauser J. Association of tumor necrosis factor – 308G/A promoter polymorphism with schizophrenia and bipolar affective disorder in a Polish population. Neuropsychobiology 2008; 57:88-94.
10. García-Miss M.d.R, Pérez-Mutul J, López-Canul B, Solis-Rodriguez F, Puga-Machado P, Oxté-Cabrera A, Gurubel-Maldonado J, Arankowsky-Sandoval G. Folate, homocysteine, interleukin-6, and tumor necrosis factor alfa levels, but not methylenetetrahydrofolate reductase C677T polymorphism, are risk factors for schizophrenia. J Psychiatric Res 2010; 4:441-6.
11. Fan X, Goff DC, Henderson DC. Inflammation and schizophrenia. Expert Rev Neurother 2007; 7:789-96.
12. Baune BT, Camara, M-L, Jawahar C, Anscomb H, Körner H. Tumour necrosis factor-alpha mediated mechanisms of cognitive dysfunctions. Transl Neurosci 2012; 3:263-77.
13. Xiu MH, Man L-J, Wang D, Du X, Yin G, Zhang Y, Tan YL, Cehn N, Cehn S, Teixeira AL, Cassidy RM, Soares JC, Zhang XY. Tumor necrosis factor-alpha -1031T/C polymorphism is associated with cognitive deficits in chronic schizophrenia patients with healthy controls. Am J Med Genet B Neuropsychiatr Genet 2018:177:379-87.
14. World Health Organization. The ICD-10 classification of mental and behavioural disorders. Geneva: World Health Organization, 1992.
15. Folstein M, Folsten S, McHugh P. Mini-mental state: a practical method for grading the cognitive state of patient for the clinician. J Psychiatry Res 1975; 12:189-98.
16. Kolegium Psikiatri Indonesia. Modul psikiatri geriatri (Geriatric psychiatry module) [in Indonesian]. Jakarta: Kolegium Psikiatri Indonesia, 2008
17. Lv MH, Tan Y.L, Yan SX, Tian L, Chen DC, Tan SP, Wang ZR, Yang FD, Yoon JH, Zunta-Soares GB, Soares JC, Zhang XY. Decreased serum TNF-alpha levels in chronic schizophrenia patients on long-term antipsychotics: correlation with psychopathology and cognition. Psychopharmacol 2015; 232:165-72.
18. Kunz M, Ceresér KM, Goi PD, Fries GR, Teixera AL, Fernandes BS, Belmonte-de-Abreu PS, Kauer-Sant'Anna M, Kapczinski F, Gama CS. Serum levels of IL-6, IL-10, TNF-α in patients with bipolar disorder and schizophrenia: differences in pro- and anti-inflammatory balance. Braz J Psychiatry 2011; 33:268-74.

19. Tian L, Tan Y, Chen D, Lv M, Tan S, Soares JC, Zhang XY. Reduced serum TNF alpha level in chronic schizophrenia patients with or without tardive dyskinesia. Prog Neuro-Psychopharmacol Biol Psychiatry 2014; 54:269-4.
20. Kubistova A, Horacek J, Novak T. Increased interleukin-6 and tumor necrosis factor alpha in first episode schizophrenia patients versus healthy controls. Psychiatr Danub 2012; 24:153-6.
21. Hope S, Melle I, Aukrust P, Steen NE, Birkenaes AB, Lorentzen S, Agartz I, Ueland T, Andreassen OA. Similar immune profile in bipolar disorder and schizophrenia: selective increase in soluble tumor necrosis factor receptor I and von Willebrand factor. Bipolar Disord 2009; 11:726-34.
22. Ochoa S, Usall J, Cobo J, Labad X, Kulkarni J. Gender differences in schizophrenia and first-episode psychosis: a comprehensive literature review. Schizophr Res Treatment 2012; 2012:916198.
23. Li R, Ma X, Wang G, Yang J, Wang C. Why sex differences in schizophrenia? J Transl Neurosci 2016; 1:37-42.
24. Chiang SSW, Riedel M, Gruber R, Müller N, Schwarz M. In vivo type II T-helper cells shift in schizophrenia compared to sex- and age-matched healthy controls. Eur J Psychiatry 2011; 25:192-204.
25. Zhu F, Zhang L, Liu F, Wu R, Guo W, Ou J, Zhang X, and Zhao J. Altered serum tumor necrosis factor and interleukin-1β in first-episode drug-naïve and chronic schizophrenia. Front Neurosci 2018; 12:296.
26. Boerrigter D, Weickert TW, Lenroot R, O'Donnell M, Galletly C, Liu D, Burgess M, Cadiz R, Jacomb I, Catss VS, Fillman SG, and Weickert CS. Using blood cytokine measures to define high inflammatory biotype of schizophrenia and schizoaffective disorder. J Neuroinflamm 2017; 14:1-15.
27. Lee EE, Hong S, Martin AS, Eyler LT, Jeste DV. Inflammation in schizophrenia: cytokine levels and their relationships to demographic and clinical variables. Am J Geriatr Psychiatry 2017; 25:50-61.
28. Ergün S, Yanartas Ö, Kandemir G, Yaman A, Yildiz M, Haklar G, and Sayar K. The relationship between psychopathology and cognitive functions with cytokines in clinically stable patients with schizophrenia. Psychiatry Clin Psychopharmacol 2018; 28:66-72.
29. Simamora RH, Loebis B, Husada MS. Comparison of serum levels of tumor necrosis factor alpha (TNF-α) in Batak male schizophrenic patients versus healthy controls. Int J Life Sci Scienti Res 2018; 4:1652-56.
30. Trovão N, Prata J, VonDoellinger O, Santos S, Barbosa M, Coelho R. Peripheral biomarkers for first-episode psychosis-opportunities from the neuroinflammatory hypothesis of schizophrenia. Psychiatry Investig 2018; 16:177-84.
31. Xu, H. Neuroinflammation in schizophrenia focused on the pharmacological and therapeutic evidence. Pharmacol 2015; 6:438-53.
32. Ter Horst R, Jaeger M, Smeekens SP, Oosting M, Swertz MA, Li Y, Kumar V, Diavatopoulos DA, Jansen AFM, Lemmers H, Toenhake-Dijkstra H, van Herwaarden AE, Janssen M, van der Molen RG, Joosten I, Sweep FCGJ, Smit JW, Netea-Maier RT, Koenders MMJF, Xavier RJ, van der Meer JWM, Dinarello CA, Pavelka N, Wijmenga C, Notebaart RA, Joosten LAB, and Netea MG. Host and environmental factors influencing individual human cytokine responses. Cell 2016; 167:1111-24.
33. Mansur RB, Zugman A, Asevedo EM, da Cunha GR, Bressan RA, Brietzke E. Cytokines in schizophrenia: possible role of anti-inflammatory medications in clinical and preclinical stages. Psychiatry Clin Neurosci 2012; 66:247-60.
34. Pollmächer T, Haack M, Schuld A, Reichenberg A, Yirmiya R. Low levels of circulating inflammatory cytokines-do they affect human brain functions? Brain Behav Immun 2002; 16:525-32.
35. Hoseth EZ, Ueland T, Dieset I, Birnbaum R, Shin JH, Kleinman JE, Hyde TM, Mørch RH, Hope S, Lekva T, Abraityte AJ, Michelsen AE, Melle I, Westlye LT, Ueland T, Djurovic S, Aukrust P, Weinberger DR, Andreassen OA. A study of TNF pathway activation in schizophrenia and bipolar disorder in plasma and brain tissue. Schizophr Bull 2017; 43:881-90.
36. Strieter RM, Kunkel SL, Bone RC. Role of tumor necrosis factor-alpha in disease state and inflammation. Crit Care Med 1993; 21:S447-63.
37. Kirkpatrick B, Miller BJ. Inflammation and schizophrenia. Schizophr Bull 2013; 39:1174-9.
38. Hennessy E, Gormley S, Lopez-Rodriguez AB, Murray C, Murray C, Cunningham C. Systemic TNF-α produce acute cognitive dysfunction and exaggerated sickness behaviour when superimposed upon progressive neurodegeneration. Brain Behav Immun 2017; 59:233-44.
39. Şahin TD, Karson A, Balci F, Yazir Y, Bayramgürler D, Utkan T. TNF-alpha inhibition prevents cognitive decline and maintains hippocampal BDNF levels in the unpredictable chronic mild stress rat model of depression. Behav Brain Res 2015; 292:233-40.
40. Belarbi K, Jopson T, Tweedie D, Arellano C, Luo W, Greig NH, and Rosi S. TNF-α protein synthesis inhibitor restores neuronal function and reverses cognitive deficits induced by chronic neuroinflammation. J Neuroinflamm 2012; 9:23.
41. Thomasy H. Tumor necrosis factor α as a potential mediator of the effects of phosphodiesterase 4B inhibition on cognition after traumatic brain injury. J Neurosci 2016; 36:11587-9.
42. Miller BJ, Culpepper N, Rapaport MH, Buckley P. Prenatal inflammation and neurodevelopment in schizophrenia: a review of human studies. Prog Neuropsychopharmacol Biol Psychiatry 2013; 42:92-100.
43. Misiak B, Stańczykiewicz B, Kotowicz K, Rybakowski JK, Samochowiec J, Frydecka D. Cytokines and C-reactive protein alterations with respect to cognitive impairment in schizophrenia and bipolar disorder: A systematic review. Schizophr Res 2018; 192:16-29.