RESEARCH ARTICLE

Comparison of Serum Levels of Tumor Necrosis Factor Alpha (TNF-α) in Batak Male Schizophrenic Patients Versus Healthy Controls

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Received: 10 Dec 2017/Revised: 17 Jan 2018/Accepted: 19 Feb 2018

ABSTRACT- Background: Schizophrenia is a common psychotic disorder, with a risk of about 1%, the etiology of schizophrenia unknown, one of which includes immunological disorders. Although, there are conflicting results, most studies focusing on plasma levels or the production of mitogen-stimulated cytokines. Furthermore, this study compared serum levels of TNF-α in male chronic schizophrenic patients and healthy control.

Methods: This cross-sectional study was conducted on 40 male patients diagnosed with chronic schizophrenic and 40 healthy control. Severity of illness was assessed with PANSS. Serum levels of TNF-α were measured by Quantikine HS Human TNF-α Immunoassay.

Results: TNF-α levels were significantly higher in chronic schizophrenic (25.12±1.76) to healthy control subjects (5.49±1.69), p=0.001; p<0.05.

Conclusion: This study suggested that TNF-α play a role in the immunopathogenesis of schizophrenia and behavioral changes. The relationship between schizophrenia and inflammation was supported by the production of abnormal cytokines.

Key-words- Batak male, Chronic schizophrenic, Healthy control, Serum TNF-α

INTRODUCTION

Schizophrenia is a common psychotic disorder, with a risk of about 1%, the most common early onset of this disease is 15-30 years of age, and is a chronic disease that causes disruption to patients and their families. [1] The exact cause of schizophrenia is not known, although several etiological theories have been proposed for the disease, including developmental or neurodegenerative processes, neurotransmitter abnormalities, viral infection and immune dysfunction or autoimmune mechanisms. [2] Schizophrenic patients have aberrant proportions of immuno-competent cells and varied levels of cytokines, especially pro-inflammatory interleukin (IL)-6, IL-1 and tumour necrosis factor (TNF)-α, in their peripheral blood or cerebrospinal fluid. [3]

Access this article online	
Quick Response Code	Website: www.ijlssr.com
	DOI: 10.21276/ijlssr.2018.4.2.6

Cytokines function as chemical messengers between immune cells and have numerous important functions in immune regulation. They also play a critical role in infectious and inflammatory processes by mediating the cross-talk between the brain and the immune system, which has been a recent focus of immunologic research in schizophrenia. [4] TNF-α production by schizophrenic patients was significantly higher than healthy controls. [5,6] In contrast to study conducted by Lv in Beijing in 2012 reported that TNF-α levels were significantly lower in patients with chronic schizophrenia relative to healthy control subjects (p<0.01). Correlation analysis revealed a significant negative correlation between the TNF-α levels and the PANSS total score (p<0.01).[7] Therefore, this study was interested in finding out whether there were differences in serum TNF-α in male patients with chronic and healthy schizophrenia control and correlation with severity of illness.

MATERIALS AND METHODS

Data source and Study sample- This study was an unpaired numerical comparative analysis used cross-sectional study, divided in two groups: Male

patients with chronic schizophrenic and healthy control group and the correlation with severity illness. Among psychiatric patients admitted in wards of the Prof. Dr. M. Ildrem Hospital, North Sumatera, Indonesia, during September 2016 to February 2017, we recruited fourty schizophrenic patients. All patients had chronic schizophrenic patients in stabilization phase of treatment at the time of study enrollment. All patients had been medication risperidone 4mg, heavy smokers, age 20-40 years old, Body Mass Index (BMI) score 18.50–24.99 kg/m2, understand the Indonesian language and willing to be a respondent and can be interviewed. Patients with a history of any concomitant psychiatric illness, such as substance or alcohol abuse, a history of chronic and acute physical condition (such as infectious or allergic diseases) associated with abnormal cell-mediated immunity or a known autoimmune disease were excluded. Fourty controls were recruited at the same hospital in the same hospital among employees, nurses and other medical personnel who working there and caregivers who come to checkup their families. Age, heavy smokers and BMI were matched between schizophrenia patients and healthy controls. Each healthy control with any personal or familial history of psychiatric illness, diagnosed autoimmune disease, chronic and acute physical illness (such as infectious or allergic diseases) associated with abnormal cell-mediated immunity, or substance or alcohol abuse were excluded. The patients gave informed consent after the procedure had been fully explained. This study was approved by the Institutional Ethical Committee of University of Sumatera Utara.

Measures

Definition of Schizophrenic- Male, who reported having been diagnosed with chronic schizophrenic by a psychiatrist; therefore, for the purposes of this study, the definition of schizophrenic is a chronic schizophrenic patient (≥5years) [8] in the stabilization phase of treatment. [9] Schizophrenic patients assessed by using "The ICD-10 classification of mental and behavioural disorders, clinical descriptions and diagnostic guidelines". [10]

Definition of severity of illness- The severity of illness was assessed using the Positive and Negative Syndrome Scale (PANSS), that is determined from the total scores PANSS to reflect the burden of illness.[11]

Definition of serum TNF-α- Tumor necrosis factor alpha (TNF –α) also known as cachectin, is the prototypic ligand of the TNF superfamily. It is a pleiotropic molecule that plays a central role in inflammation, immune system development, apoptosis, and lipid metabolism. In this study, serum TNFα levels were measured by Quantikine HS Human TNF-α Immunoassay which is a 6.5-hour solid-phase ELISA designed to measure TNF-α in serum and plasma [12].

Covariates- Sociodemographic characteristics included age, marital status was coded into two categories (Married or Unmarried), and educational level education was categorized as junior high school, senior high school, and college, and ethnic group was categorized Bataknese or Non-Bataknese. Chronic and acute physical condition assessed via the health interview (such as infectious or allergic diseases). Heavy smokers were defined the status of smoking exposure (>20 cigarettes daily).[13] Body mass Index (BMI) was calculated using measurements of subjects weight and height [weight (kg)/height (m^2)]. Normal was considered present if subjects had a BMI of 18.50–24.99 kg/m^2.[14]

Statistical Analysis- Serum levels of TNF-α s in both groups were analyzed using unpaired T-test , If the serum levels of TNF-α were normally distributed both in schizophrenic patients and controls (Saphiro-Wilk test, $p>0.05$). The significance level was set at $p<0.05$ for all analysis. [15]

RESULTS

Socio-demographic characteristics- Of the 80 male subjects included in this study and divided into two groups: 40 subjects had been diagnosed with chronic schizophrenic by psychiatrist and 40 subjects as healthy control group. The mean age in the schizophrenic group (33.80±3.51) and control group (34.43±3.59). Based on marital status, the schizophrenic group married 27 (21.60%) more than unmarried subjects, and healthy control group the most was married subject 24 (19.20%). In both the schizophrenic group and healthy control group the most were Bataknese ethnic groups. The mean body mass index in the schizophrenic group was 21.61±2.01, and healthy control group was 21.13±1.86. There were no significant differences in age, marital status, ethnic group, and BMI between the groups ($p>0.05$).

In schizophrenic group, highest level of education was junior high school (47.50%) and in healthy group was college (42.50%). There were significant differences in education ($p<0.05$), but education did not significantly affect serum levels of TNF-α.

Comparison Serum Levels of Tumor Necrosis Factor Alpha in Batak Male Patients with Chronic Schizophrenic versus Healthy Control

Serum levels of TNF-α in male patients with chronic schizophrenic (25.12±1.76) was significantly higher than healthy controls group (5.48±1.68) by using independent T-test, there were significant difference between the mean TNF-α between the schizophrenic and healthy control groups ($p=0.001$; $p<0.05$).

Table 1: Demographic characteristic of the samples according to the group

Variable	Schizophrenic (n_1)	Healthy control (n_2)	p-value
Age (years old)	33.80± 3.51	34.43 ± 3.59	0.433[a]
Marital status			
Married	13.00 (10.40)	16.00 (12.80)	0.845[b]
Unmarried	27.00 (21.60)	24.00 (19.20)	
Education			
Junior High School	19.00 (47.50)	8.00 (20.00)	0.008[b]
Senior High School	15.00 (37.50)	15.00 (37.50)	
College	6.00 (15.00)	17.00 (42.50)	
Body Mass Index (Kg/m^2)	21.61 ± 2.01	21.13 ± 1.86	0.299[c]

[a]Independen T test, [b]Chi Square, [c]Mann Whitney U test

Table 2: Serum levels of TNF-α in Batak male patient with chronic Schizophrenic and healthy control group

Variable	Serum Levels of TNF-α (mean ± s.d)	Mean difference (95% Confidence interval)	p-value
Chronic Schizophrenic (n_1)	25.12±1.76	19.63 (18.86-20.40)	0.001*
Healthy Control group (n_2)	5.49±1.69		

*** Independent T test**

DISCUSSION

The main findings of the present study were that serum levels of TNF-α level was significantly higher in male patients with chronic schizophrenia than in healthy control subjects, and there were significant positive correlations between serum levels of TNF-α and the total PANSS score. We demonstrated that pro-inflammatory cytokines TNF-α were significantly higher in schizophrenic patients as compared to healthy controls. These results were consistent with some previous studies that showed higher production of TNF-α in schizophrenic patients. Miller et al. and Potvin et al. reported that in creation of serum levels of TNF-α alpha is reciprocal with the well-described pro-inflammatory state in schizophrenia. Increased TNF-α were proinflammatory mediators produced predominantly by macrophages.[16,17] Several studies have proved increased plasma cytokine levels or mitogen-stimulated cytokine production in schizophrenia such as TNF-α [18].

Increased plasma levels of TNF associated with schizophrenia was also confirmed by Na and Kim [5] in Korea and Theodoropoulou et al. in Athens showed the levels of TNF-α were significantly higher in chronic schizophrenic patients compared with healthy controls ($p < 0.001$).[5,6] Kubistova *et al.* [19] measuring elevated serum levels of TNF-α in schizophrenic and healthy controls pre and post treatment found significant differences in serum levels of TNF-α were higher in the schizophrenic group compared with controls both before and after treatment. The significant correlation between PANSS subscales for positive and negative subscales and the total PANSS score or between the differences in psychopathology and cytokine levels before and after treatment. Al- Asmari observed serum levels of TNF-α of schizophrenic patients were significantly higher than those of healthy controls. The different activities of inflammatory cytokines in schizophrenic patients suggest that specific subtypes of cytokines, monocytic pro-inflammatory cytokines, may be associated with the immune-pathogenesis of schizophrenia.[20] Ajami *et al.* [21] reported serum levels TNF-α in schizophrenic higher than healthy control. They concluded an increase in TNF-α may have an important role in schizophrenic psychopathology.

In contrast with Zhang *et al.* [22] measured the cytokine levels including TNF-α in chronic schizophrenic patients who smoked with long-term antipsychotic use found no significant difference in serum levels of TNF-α in chronic schizophrenic patients who smoked (10.1±1.8) and non-smoke (10.7±2.7); p=0.28. Nevertheless they argue in accordance with previous studies that schizophrenia is characterized by activation of proinflammatory cytokines such as TNF-α. TNF-α is a cytokine involved in systemic inflammation and is a member of a group of cytokines which stimulate acute phase reactions. A chronic immune activation in schizophrenia had been shown elsewhere.[23] TNF-α is a ubiquitous pro-inflammatory cytokine elevated in immune response. TNF-α might contribute to the pathogenesis of schizophrenia by activation of the hypothalamo-pituitary-adrenocortical (HPA) axis, activation of neuronal serotonin transporters, stimulation of the indoleamine 2,3-dioxygenase which leads to tryptophan depletion and activation of kynurenine metabolites, or by the neurotoxic release of glutamate [24]. The etiology and pathophysiology of schizophrenia had

not been clearly defined. Some changes in the central nervous system can cause clinical manifestations of this disease include Brain-derived Neurotropic Factor (BDNF) [25], vitamin D levels in the blood, [26] and TNF-α.[23] In addition, cytokines might cross the blood–brain barrier (BBB) either through leaky areas or by active transport. Increased permeability of the BBB may enable activated immune or neurotoxic cytokines to enter the CNS and trigger psychopathological changes.[20]

CONCLUSIONS

This study suggested that TNF-α maybe play important roles in the patho-physiology of schizophrenia and may be a marker of schizophrenia. There is a growing evidence base supporting the role of inflammation in the etiology of schizophrenia. TNF-α might contribute to the pathogenesis of schizophrenia by activation of the HPA axis, activation of neuronal serotonin transporters, stimulation of the indoleamine 2,3-dioxygenase which leads to tryptophan depletion and activation of kynurenine metabolites, or by the neurotoxic release of glutamate and cytokines might cross the blood–brain barrier (BBB). Although, many studies reported, immunological findings in schizophrenia but are still often contradictory. Variables that may be confounding in studies are important for control, including disease length, treatment received, comorbidities and additional factors that may be biased variables. So the evidence that changes in cytokine levels occur in schizophrenia is still needed.

ACKNOWLEDGMENT

Authors, who wishing to thank the infinite thanks for help or encouragement from supervisors, resident colleagues, all technical staff, and families who have provided moral and material support so that this paper can be completed.

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How to cite this article:

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(2): 1652-1656. DOI:10.21276/ijlssr.2018.4.2.6