Majalah Kedokteran Andalas
Vol. 46, No. 8, Januari 2024, Hal. 1272-1281
http://jurnalmka.fk.unand.ac.id

ARTIKEL PENELITIAN

Correlation between Cognitive Function and Serum Levels of Tumor Necrosis Alpha (TNF-α) in Schizophernia

Eldi Sauma[1], Antania Hanjani Irianti[2], Tuti Kurnianingsih[2,4], Shelly Iskandar[2], Sumartini Dewi[3,4], Veranita Pandia[2,4]

1. Psychiatry Department, Medical Faculty, Universitas Andalas, West Sumatera, Indonesia; 2. Psychiatry Department, Medical Faculty, Universitas Padjajaran, West Java, Indonesia; 3. Internal Medicine Department, Medical Faculty, Universitas Padjajaran, West Java, Indonesia; 4. Immunology Central Study, Medical Faculty, Universitas Padjajaran, West Java, Indonesia

Korespondensi: *Eldi Sauma, email: eldisauma@gmail.com. phone: 08116624422*

Abstrak

Tujuan: Penelitian ini bertujuan untuk menganalisis hubungan fungsi kognitif dengan kadar TNF-α serum pada pasien skizofrenia di Indonesia. **Metode:** Penelitian ini merupakan penelitian analitik dengan desain cross-sectional pada 34 pasien skizofrenia yang dirawat di Rumah Sakit Jiwa Provinsi Jawa Barat. Pasien dengan risiko peradangan dan gangguan kognitif tidak disertakan. Fungsi kognitif dinilai menggunakan Rey Auditory Verbal Learning Test (RAVLT), Digit Span dan Trail Making Test. Kadar TNF-α serum diukur menggunakan metode Sandwitch-ELISA (Enzyme-linked Immunosorbent Assay). **Hasil:** Peserta penelitian menunjukkan adanya defisit kognitif pada seluruh instrumen ujian. Kadar TNF-α serum peserta meningkat (rata-rata: 8,93 ± 3,43). Kadar TNF-α serum tidak berkorelasi signifikan dengan fungsi kognitif. **Kesimpulan:** Tidak terdapat hubungan bermakna antara fungsi kognitif dengan kadar TNF-α serum pada skizofrenia.
Kata kunci: Skizofrenia; fungsi kognitif; TNF-α

Abstract

Objective: *This study aims to analyze the correlation between cognitive function and TNF-α serum levels in schizophrenic patients in Indonesia.* ***Methods:*** *This study is an analytical study using a cross-sectional design in 34 schizophrenic patients who were hospitalized in the Mental Hospital of West Java Province. Patients with risk of inflammation and cognitive impairment are excluded. Cognitive function was assessed using the Rey Auditory Verbal Learning Test (RAVLT), Digit Span and Trail Making Test. TNF-α serum levels were measured using the Sandwitch-ELISA (Enzyme-linked Immunosorbent Assay) method.* ***Results:*** *Study participants showed a cognitive deficit in all examination instruments. The TNF-α serum levels of the participants increased (mean: 8.93 ± 3.43). TNF-α serum levels was not significantly correlated with cognitive function.* ***Conclusion:*** *There is no significant correlation exist between cognitive function and TNF-α serum levels in schizophrenia.*
Keywords: *PD-L1; LSCC; differentiation; staging*

INTRODUCTION

Schizophrenia is a unique disorder consisting of a complex set of neurophysiological, neurochemical, and psychological disorders. Signs and symptoms are vary, including changes in perception, emotions, cognition, thinking, and behavior[1,2]

The prevalence of schizophrenia in the world is known to be 1%, with a lifetime prevalence of 0.6 to 1.9 percent according to the Epidemiologic Catchment Area (ECA) study. Data from the World Health Organization (WHO) in 2019 states that schizophrenia affects more than 20 million people worldwide. Meanwhile in Indonesia, according to basic health research data in 2018, the prevalence of schizophrenia was 6.7‰, with a prevalence in West Java of 5‰.[1–4]

Schizophrenia begins at a young age and can cause significant long-term impairment, requiring repeated hospital admissions, ongoing clinical care and rehabilitation. This condition increases the financial burden for patients and families. In the United States it has been reported that the financial costs of schizophrenia are estimated to exceed the financial burden of all cancers combined. And in the course of their illness, schizophrenic patients who experience impaired cognitive function further worsen their clinical condition and increase their care burden.[1,2]

Impaired cognitive function in schizophrenia is a major contributor to the patient's inability to function adequately in daily life. Impaired cognitive function occurs in more than 70% of schizophrenia patients. Cognition is a high-level brain function that describes the mental process of gaining knowledge and understanding through thoughts, experiences, and senses. Cognition consists of working memory, understanding and producing language, calculating, reasoning, problem solving, and decision making. Cognitive abilities depend on the integrity of basic functions, such as motor, sensory, and autonomic functions, as well as the patient's emotional state.[5,6]

This condition is the main cause of disability in occupational, social and economic functions in schizophrenic patients, so it must be an important therapeutic target in patient management, while existing therapy is not yet effective for impaired cognitive function in schizophrenic patients.[1,2,7–9]

Several hypotheses explain the etiology of schizophrenia, one of which is the theory of inflammation. Inflammation in the central nervous system (CNS) is closely linked to neurodegeneration. In addition to proinflammatory cytokines, microglia also play an important role in inflammatory processes in the CNS. Uncontrolled activity of proinflammatory cytokines and microglia, together with genetic susceptibility and glutamatergic neurotransmitters can lead to schizophrenia.[10–12]

One of the cytokines that is often associated with impaired cognitive function in schizophrenia is TNF-α. Various previous studies linking TNF-α and cognition in individuals with schizophrenia showed inconsistent results, especially in the variability of the cognitive measures used in the studies, research by Zhang et al. (2016) assessed cognition via interview-based PANSS cognitive factors, while previous research has suggested measuring verbal skills rather than

neurocognition (Nielsen et al., 2014; Ehmann et al., 2004). Likewise, Goldsmith et al., 2018 showed that increased TNF-α in individuals with schizophrenia was associated with cognitive impairment, but their study did not examine neurocognition.[10,13]

Levels of proinflammatory cytokines including TNF-α can be influenced by genetic and racial factors. In Indonesia itself, no research has been published regarding the correlation of cognitive function with serum levels of TNF-α in schizophrenia.[11] Therefore, the author wants to examine the correlation between cognitive function and serum levels of TNF-α in schizophrenia with the Indonesian population, using an instrument that can measure cognitive function, both verbal and neurocognitive, and its relation to daily function, so that we can see the correlation between cognitive function and serum levels of TNF-α more thoroughly.

Therefore, the author wants to examine the correlation between cognitive function and serum levels of TNF-α in schizophrenia with the Indonesian population, using an instrument that can measure cognitive function, both verbal and neurocognitive, and its relation to daily function, so that we can see the correlation between cognitive function and serum levels of TNF-α more thoroughly.

METHODS

. Sample selection was carried out using the inclusion criteria: patients diagnosed with schizophrenia based on DSM V, aged 18-45 years, male, using antipsychotic medication, able to speak Indonesian, and the family had agreed for the patient to take part in the research. Patients who experience intellectual disabilities, are uncooperative and anxious, have neurological disorders (delirium, dementia, stroke and post-stroke) which can affect cognitive function, use anti-inflammatory drugs, suffer from acute infectious diseases, autoimmune diseases, allergies, tumors, metabolic syndrome, or had a history of substance and alcohol abuse in the last one year were not included in this study. The research was carried out by examining cognitive function using a cognitive function examination instrument, namely the Rey Auditory Verbal Learning Test (RAVLT), which consists of the Rey Auditory Verbal Learning Test – Immediate (RAVLT-I) and the Rey Auditory Verbal Learning Test – Delayed (RAVLT-D) , Digit Span and Trail Making Test (TMT) which consists of Trail Making Test - A (TMT-A) and Trail Making Test - B (TMT-B). The blood test is carried out one day after the cognitive function test, provided the patient has fasted for at least 10 hours before the blood test (can only drink water without sugar) to measure serum levels of TNF-α, leukocytes, HDL cholesterol and fasting blood glucose. Data analysis uses the Statistical Package for the Social Science (SPSS) application to assess the correlation between variables. Correlation analysis uses Guilford criteria to assess the direction and level of correlation.

RESULTS AND DISCUSSION

A total of 121 patients who were hospitalized at the West Java Provincial Mental Hospital in June and July 2020 were screened using medical record data and interviews with patients and families. There were 34 patients who met the inclusion and exclusion criteria. The

characteristics of the research subjects can be seen in table 1.

Table 1 shows that the average age of the subjects was 33 years, and the average BMI of the subjects was 21.28 ± 3.48, with the majority of subjects having normal body weight (61.8%). Most of the subjects had a high school education or equivalent (41.2%), unemployed (58.8%), and were not married (61.8%). A total of 88.2% of subjects were smoker with the median number of cigarettes per day being 12 cigarettes. Most patients had a disease duration of 6 to 10 years (32.4%). There were the same number of subjects who had been treated for the first time and subjects who had been treated more than twice (35.5%). Most subjects received combination antipsychotics (67.6%) and did not receive trihexyphenidyl (70.6%).

Table 2 shows the characteristics of the cognitive function of the research subjects. From the table it can be concluded that in general there is a cognitive deficit in the research subjects. The results of the examination using RAVLT-I, in the first trial 26 subjects (76.5%) experienced cognitive deficits, in the 2nd trial 31 subjects (91.2%) experienced cognitive deficits, and in the 3rd trial 33 subjects (97.1%) experienced cognitive deficits, while the RAVLT-D (recall) showed 32 subjects (94.1%) experienced cognitive deficits. In the examination using the digit span instrument, it was found that the results of the digit span forward examination showed that 19 subjects (55.9%) had cognitive deficits, and in the examination of the digit span backwards it was found that 33 subjects (97.1%) had cognitive deficits. There were 23 subjects who experienced cognitive deficits when examined with TMT-A and 18 subjects (52.9%) when examined with TMT-B.

Examination using the RAVLT instrument is useful for assessing verbal memory abilities, where RAVLT-I shows immediate verbal memory abilities and RAVLT-D provides an overview of delayed verbal memory abilities.[14,15]

The results of this research indicated a deficit in immediate and delayed verbal memory in the research subjects, which can be seen from the average RAVLT-I score (both in trials 1, 2 or 3) and the average RAVLT-D score which is below normal. However, there is still an increase in the average score for each RAVLT-I examination, namely the average for the first examination is 3.5; second examination 4.0; and the third examination 4.3. The increase in score results in this study shows that the learning process is still occurring in the subjects of this study. The results of this study are similar with previous research by Johanna, et al, 2011, which said that verbal memory is the cognitive domain most impaired in schizophrenia. The disorder can be present in first and chronic episodes of schizophrenia patients and can be found throughout the course of the disease. The increase in score results in this study is in accordance with the research of Normala et al. This study showed that there was an increase in the average RAVLT-I at the fifth examination (score 10) compared to the first examination (score 4) in schizophrenia patients, but the overall score for schizophrenia patients was lower than normal subjects.[16–18]

Cognitive examination using the digit span instrument can assess 2 things, where digit span forward can provide an overview of the subject's attentional abilities and digit span backward provides

an overview of the subject's working memory. In this study, it was found that 55.9% of research subjects experienced deficits in attention as seen from digit span forward examination scores which were below normal. Attention is indeed one of the cognitive domains that is disturbed in schizophrenia. Disturbances in attention result in difficulty following social conversations and an inability to follow important instructions; Simple activities that require attention such as reading or watching television become difficult. Attention disorders can interfere with many other cognitive functions, because poor attention will result in many types of information could not properly processed.[19,20]

As many as 97.1% of the subjects in this study showed examination results with digit span backward below normal. This means that there is a working memory deficit in the subjects of this research. Working memory is the cognitive system responsible for temporarily storing information available for processing. Working memory is important for reasoning and guiding decision making and behavior. In various literatures working memory is mentioned as a core component of cognitive deficits in schizophrenia.[21,22]

TMT is an instrument that can provide a good description of cognitive function. The TMT-A tests a person's ability in processing speed, and the TMT-B tests reasoning and problem-solving abilities. In the subjects of this study, when the TMT-A examination was carried out, it was found that 67.6% of the subjects had deficits in processing speed, and when the TMT-B examination was carried out, it was found that 52.9% of the subjects had deficits in reasoning and problem solving.

Processing speed is a cognitive ability defined as the time it takes a person to perform a mental task. It is related to the speed at which a person can understand and react to the information they receive. Reasoning itself includes the cognitive procedures we use to make conclusions from knowledge. While problem solving includes a series of cognitive procedures and thought processes that we apply to achieve a goal when we have to overcome obstacles to achieve that goal. Reasoning can be part of problem solving. And all three are impaired in schizophrenic patients.[19,20]

Table 3 shows that 91.2% of subjects had serum levels of TNF-α above 2.9pg/ml, with the average subject serum TNF-α level being 8.93pg/ml, which indicates that there was an increase in serum levels above normal. The results of this study are in accordance with several previous studies. In the research of Kim et al. (2009) regarding changes in cytokines and tryptophan metabolites in first-onset schizophrenia patients or who had not received treatment for at least 4 months, found significantly higher levels of TNF-α in schizophrenia patients who had not received treatment compared to schizophrenia patients after receiving antipsychotic treatment for 6 weeks. . Pandey et al. (2015) who examined proinflammatory cytokines in schizophrenia patients and their membrane-bound receptors found that TNF-α mRNA levels and protein expression were significantly increased in lymphocytes of schizophrenia patients compared to normal control subjects. Research conducted by Pandey et al. (2015) shows that in addition to the increase in proinflammatory cytokines and their soluble receptors in the plasma of schizophrenia patients, abnormal gene

expression and membrane-bound TNF-α receptors may be involved in the pathogenesis of schizophrenia..[23,24]

TNF-α levels can be influenced by various factors, including: use of anti-inflammatory drugs, acute infectious diseases, autoimmune diseases, allergies, tumors and metabolic syndrome. In this study, factors that influenced TNF-α levels were minimized by conducting screening through examination of medical records, interviews, physical examinations and laboratory examinations.

From the data obtained, a correlation analysis was carried out between cognitive function and the subject's serum levels of TNF-α. Table 4 shows that there is no significant correlation ($p>0.05$) between cognitive function and the subjects' serum levels of TNF-α. Most of the correlations between cognitive function and the subject's serum levels of TNF-α showed very weak positive correlations, meaning that the better the cognitive function, the higher the subject's serum levels of TNF-α. Only on the digit span forward examination, the results showed that there was a very weak negative correlation ($r = -0.026$) between cognitive function and the subject's serum levels of TNF-α, which means that the lower the digit span forward examination result, the higher the subject's serum levels of TNF-α. however, this correlation is not statistically significant ($p=0.443$).

This study is the first study to link the cognitive function of schizophrenia patients, which was measured using three measurement instruments, namely RAVLT, Digit Span and TMT, with serum levels of TNF-α. This study did not find a significant correlation between cognitive function and serum levels of TNF-α in schizophrenic patients. The results of this study are not in compliamce with the results of research by Meng et al (2015) which found that there was a significant negative correlation between TNF-α levels and cognitive subscales in schizophrenic patients. This discrepancy may be due to differences in sample size and differences in the cognitive instruments used in Meng et al's research, namely the cognitive subscale of the PANSS examination.[25]

The results of this study are also not in accordance with research by Kogan et al (2018) which examined inflammation in schizophrenic patients and its effect on neurocognition, which found that there was a significant negative correlation between TNF-α levels and cognitive function in schizophrenia patients. This discrepancy is also caused by differences in sample size and differences in the use of different cognitive instruments where the research by Kogan et al used the MATRICS Consensus Cognitive Battery (MCCB). The MCCB is the most recommended cognitive instrument for cognitive examination in schizophrenia because it is specifically for the schizophrenia population, but this instrument has not been fully validated in Indonesia.[13]

It is known that cognitive impairment in schizophrenia occurs in the prodromal stage and remains stable throughout life, several studies have shown variations in cognitive test results at different phases of the disease, the more chronic the course of the disease, the more the cognitive function performance of schizophrenic patients decreases.[1,9] Considering this, the results of this study may be influenced by these confounding factors, because in this study the duration of illness in the research subjects was not uniform.

Further analysis was carried out by correlating cognitive function with subject

characteristics. Table 5 shows that there is a significant relationship between cognitive function and education on all examination instruments ($p<0.05$), namely that the higher the patient's education level, the better their cognitive function. The type of pharmacotherapy (typical, atypical, or combination antipsychotic) and administration of trihexyphenidyl were associated with cognitive scores examined with RAVLT-I, backward digit span, TMT-A and TMT-B. Length of hospitalization history only correlated with TMT-A ($p=0.004$).

According to research by Akiyama, et al. (2016) cognitive function can be influenced by the patient's premorbid IQ. Meanwhile research by Ohi, et al (2019) found a decrease in the IQ of schizophrenic patients when compared between premorbid IQ and IQ when they were already suffering from schizophrenia. Because in this study there was no data on premorbid IQ or current IQ, this could be a confounding factor in this study. [26,27]

Mohn, et al. (2014) examined the relationship between IQ and cognitive function in healthy people, finding that there was a significant correlation between IQ and cognitive function, namely the higher the IQ, the better the cognitive function of their research subjects. In their research, Mohn, et al also found that the higher the level of education, the higher the IQ of their research subjects. These two things are confounders in this research, because there is no IQ data on research subjects and the subjects' education levels are also not uniform. [28]

Trihexyphenidyl as an anticholinergic drug can reduce cognitive function due to its action which reduces cholinergic transmission which causes a decrease in acetylcholine activity which plays a very important role in attention, individual response, storage processes and memory retrieval. Research by Sethienluckana, et al (2018) found an increase in the cognitive performance of schizophrenia patients after stopping the use of trihexyphenidyl.[29] The subject's education level had a statistically significant correlation ($p<0.05$) for each type of cognitive examination, including RAVLT, digit span and TMT examinations. The number of hospitalizations showed a significant moderate negative correlation ($r = -0.450$, $p = 0.004$) with the results of the TMT-A examination. This shows that these factors are confounders in this study because in this study there was no uniformity in the education and type of pharmacotherapy received by patients.[13,29]

In this research, we eliminated confounding factor that could interfere cognitive function which is examination for metabolic syndrome.

CONCLUSION

This research is the first study to link the cognitive function of schizophrenia patients, which was measured using three measurement instruments, namely RAVLT, Digit Span and TMT, with serum levels of TNF-α. This study shows that there is an increase in serum TNF-α levels in schizophrenic patients. The results of the examination showed that there was a deficit in cognitive function in schizophrenic patients, and there was an increase in test results when repeated. Correlation analysis showed that there was no significant correlation between serum levels of TNF-α and cognitive function in schizophrenia patients. Further

analysis needs to be carried out by eliminating various confounding factors.

FINANCIAL SUPPORT

This research was supported by the Indonesian Education Fund Management Institute (LPDP).

ACKNOWLEDGEMENT

Much obliged to Padjajaran University and West Java Province Mental Hospital for the support for this research.

CONFLICT OF INTEREST

There is no conflict of interests in this research.

REFERENCES

1. Sadock B, Sadock V, Ruiz P. *Kaplan and Sadock's Synopsis of Psychiatry: Behavioral Sciences/Clinical Psychiatry*. 11th ed. Wolter Kluwer; 2015.
2. Kupfer D. *The American Psychiatric Publishing Textbook of Psychiatry*. 6th ed. American Psychiatric Pub; 2014.
3. Riset Kesehatan Dasar. Hasil Utama Riskesdas 2018. *Kementrian Kesehat Republik Indones*. Published online 2018:1-100. doi:1 Desember 2013
4. World Health Organization (WHO). Schizophrenia. Published 2019. https://www.who.int/mental_health/management/schizophrenia/en/
5. Winn H, Youmans J. *Youmans and Winn Neurological Surgery*. 7th ed. Elsevier; 2017.
6. Shmukler A, Gurovich I, Agius M, Zaytseva Y. Long-term trajectories of cognitive deficits in schizophrenia: A critical overview. *Eur Psychiatry*. 2015;30(8):1002-1010.
7. Harvey P, Bowie C. Cognitive enhancement in schizophrenia: pharmacological and cognitive remediation approaches. *Psychiatr Clin*. 2012;35(3):683-698.
8. Mihaljevic-Peles A, Bajs Janovic M, Sagud M, Zivkovic M, Janovic S, Jevtovic S. Cognitive deficit in schizophrenia: an overview. *Psychiatr Danub*. 2019;31(2):139-142.
9. Stahl S. *Stahl's Essential Psychopharmacology: Neuroscientific Basis and Practical Applications*. 4th ed. Cambridge university press; 2013.
10. Fineberg A, Ellman L. Inflammatory cytokines and neurological and neurocognitive alterations in the course of schizophrenia. *Biol Psychiatry*. 2013;73(10):951-966.
11. Girgis R, Kumar S, Brown A. The cytokine model of schizophrenia: emerging therapeutic strategies. *Biol Psychiatry*. 2014;75(4):292-299.
12. Na K, Jung H, Kim Y. The role of pro-inflammatory cytokines in the neuroinflammation and neurogenesis of schizophrenia. *Prog Neuropsychopharmacol Biol Psychiatry*. 2014;3(48):277-286.
13. Kogan S, Ospina L, Kimhy D. Inflammation in individuals with schizophrenia–Implications for

neurocognition and daily function. *Brain Behav Immun*. 2018;74:296-299.
14. Moradi E, Hallikainen I, Hänninen T, Tohka J. Rey's Auditory Verbal Learning Test scores can be predicted from whole brain MRI in Alzheimer's disease. *NeuroImage Clin*. 2017;13:415-427.
15. Schmidt M. *Rey Auditory Verbal Learning Test: RAVLT : A Handbook.Western Psychological Services*.; 1996.
16. Manglam M, Das A. Verbal learning and memory and psychopathology in schizophrenia. *Asian J Psychiatr*. 2013;6(5):417-420.
17. Laere E, Tee S, Tang P. Assessment of Cognition in Schizophrenia Using Trail Making Test: A Meta-Analysis. *Psychiatry Investig*. 2018;15(10):945-955.
18. Keefe R, Harvey P. Cognitive impairment in schizophrenia. *Handb Exp Pharmacol*. 2012;213:11-37.
19. Bhattacharya K. Cognitive function in schizophrenia: A review. *J Psychiatry*. 2015;18(1):14-78.
20. Harvey P, Isner E. Cognition, Social Cognition, and Functional Capacity in Early-Onset Schizophrenia. In: *Child and Adolescent Psychiatric Clinics*. ; 2019.
21. Fujii K, Yoshihara Y, Matsumoto Y, et al. Cognition and interpersonal coordination of patients with schizophrenia who have sports habits. *PLoS One*. 2020;5(11).
22. Kim Y, Myint A, Verkerk R, Scharpe S, Steinbusch H, Leonard B. Cytokine changes and tryptophan metabolites in medication-naïve and medication-free schizophrenic patients. *Neuropsychobiology*. 2009;59(2):123-129.
23. Pandey G, Ren X, Rizavi H, Zhang H. Proinflammatory cytokines and their membrane-bound receptors are altered in the lymphocytes of schizophrenia patients. *Schizophr Res*. 2015;164(1-3):193-198.
24. Lv M, Tan Y, Yan S, et al. Decreased serum TNF-alpha levels in chronic schizophrenia patients on long-term antipsychotics: correlation with psychopathology and cognition. *Psychopharmacology (Berl)*. 2015;232(1):165-172.
25. Akiyama K, Saito S, Saito A, et al. Predictive value of premorbid IQ, negative symptoms, and age for cognitive and social functions in Japanese patients with schizophrenia: A study using the Japanese version of the Brief Assessment of Cognition in Schizophrenia. *Psychiatry Res*. 2016;246:663-671.
26. Ohi K, Shimada T, Kataoka Y, et al. Intelligence decline between present and premorbid IQ in schizophrenia: Schizophrenia Non-Affected Relative Project (SNARP). *Eur Neuropsychopharmacol*. 2019;29(5):653-51.
27. Mohn C, Sundet K, Rund B. The relationship between IQ and performance on the MATRICS consensus cognitive battery. *Schizophr Res Cogn*. 2014;1(2):96-100
28. Sathienluckana T, Unaharassamee W, Suthisisang C, Suanchang O, Suansanae T. Anticholinergic discontinuation and cognitive functions in patients with schizophrenia: a pharmacist-physician collaboration in the outpatient department. *Integr*

Pharm Res Pract. 2018;7(161-171).