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Differences between Tumor Necrosis Factor-Alpha Levels and Interleukin-2 Levels in people with schizophrenia who get risperidone drugs in the acute phase of treatment in the Prof. DR. M. Ildrem Psychiatric Hospital, Medan

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Abstract

AIM: We looked for differences between tumor necrosis factor (TNF)-alpha and interleukin-2 (IL) levels in people with schizophrenia who got risperidone medication in the acute phase of treatment at Prof. Dr. M. Ildrem Psychiatric Hospital, Medan.

METHODS: We conducted a cross-sectional study that included 40 subjects. This study is a numerical comparative analytical study not paired with a single measurement with subject retrieval performed in a non-probability sampling method of consecutive sampling type.

RESULTS: The analysis test results showed that median levels of TNF-α in the group of people with schizophrenia were obtained at 3.40 with a minimum score of 0.65 and with a maximum score of 43.8 while in the healthy control group, the median score of TNF-α levels was 14.75 with a minimum score of 5.18 and a maximum score of 31.1. The average IL-2 level in people with schizophrenia was found at 5.26 with a standard deviation of ±0.987 and at the control was obtained at 3.43 with a standard deviation ± 0.665.

CONCLUSIONS: There is a significant difference in TNF-α levels between groups of people with schizophrenia who get risperidone 4 mg in the acute phase of treatment and control. There was a significant difference between IL-2 levels between people with schizophrenia who got risperidone 4 mg in the acute phase of treatment and control.

Introduction

Schizophrenia is a chronic and severe mental disorder that affects more than 21 million people in the world. Schizophrenia is characterized by distortions in thinking, perception, emotion, language, and behavior. Common experiences include hallucinations – hearing voices or seeing things that do not exist and delusions – wrong and fixed beliefs [1].

Worldwide, schizophrenia is associated with considerable disability and can affect educational and employment performance. People with schizophrenia are 2–3 times more likely to die earlier than the general population. It is often caused by preventable physical diseases, such as cardiovascular disease, metabolic diseases, and infections. Schizophrenia is treatable. Treatment with drugs and adequate psycho-social support assisted living facilities, supported housing, and supported work is effective management strategies for people with schizophrenia. Assisted living facilities, supported housing, and supported work are effective management strategies for people with schizophrenia [1].

Schizophrenia is a highly heterogeneous disorder, and some investigators have suggested that immune abnormalities may be involved in the etiology and pathophysiology of schizophrenia [2].

Cytokines are proteins secreted by different cells and perform paracrine, endocrine, and even autocrine functions. They can relatively penetrate the blood–brain barrier and bind to their receptors in neurons and glial cells. Furthermore, cytokines can be produced in the central nervous system (CNS). Although many cytokines are secreted by glial cells in the brain, some documents reveal that neurons can also produce cytokines under certain conditions [3].

Cytokines serve as carriers of chemicals among immune cells and have many essential functions in immune settings. They also play a critical role in the infectious and inflammatory processes by mediating cross-talk between the brain and the immune system, which has been the focus of recent immunological research in schizophrenia [2].

Necrosis factor (tumor necrosis factor [TNF]-alpha) tumors are synthesized in CNS and have an essential role in moderating the growth, differentiation, and application of glutamatergic, serotonergic, and dopaminergic pathways [4].

Methods

Patient sample

This study used comparative numerical analysis not paired with a single measurement, subject retrieval by non-probability sampling, consecutive sampling, and has been done by taking a sample of 40 people with schizophrenia in the Prof. Dr. M. Ildrem Psychiatric Hospital, Medan, who was diagnosed based on ICD-10 criteria, aged 18–45 years, using the anti-psychotic drug risperidone 4 mg. The exclusion criteria were the absence of a history of common medical disorders and other psychiatric disorders. Forty healthy control samples around the University of North Sumatra that were willing to be the subject of research. The study was conducted between October 2019 and December 2019.

Biological Studies

Blood samples for examination were collected in the morning between 7 and 9 PM after the subject had previously served the fast. Patients have fasted at least 10–12 h. Prepare tools and materials. Label the identity on the blood tubes of the research subjects. Using a hands-on and installing a tourniquet at 3–4 inches from the location of the function, the subject was then asked to clench his palm until the vein was visible. Clean the area of the function on the median cubital vein on the folding elbow with gauze and 70% alcohol swab by rotating from the inside out and letting the location dry. Plasma, that is, blood, should be taken using standard venipuncture techniques and plasma collected using sodium citrate, EDTA, or heparin as anticoagulants. To ensure optimal recovery and minimal platelet contamination, after collection, there should be a rapid separation of plasma with less than 30 min on ice and centrifuge for 10 min to remove any particles. Avoid hemolytic, lipid, or murky samples that were too dirty, samples should be used immediately. Otherwise, samples should be specially made and stored at a temperature of −20°C to avoid loss of bioactivity and contamination. TNF-α levels were measured in serum from duplicated by the enzyme-linked immunosorbent assay (ELISA) method of TNF-α special kits. Previously, the serum was separated by centrifugation method and stored in freezing conditions at −20°C until ELISA examination. The inspection followed instructions given by the kit maker.

Statistical Analysis

Analysis of the data collected using the Statistical Package for Service Solution (SPSS ver. 22) software program. Categorical variable data were presented in sum (n) and percentage (%). Variable of gender, employment status, and marital status was categorical variables tested with unpaired categorical comparative table 2 × 2 where the Chi-square testing conditions, thus incorporated Pearson Chi-square score. The educational status variable was a categorical variable, tested by unpaired categorical comparative 2 × 3 table, where the Chi-square testing requirement was met so that it is entered a Pearson Chi-square score.

Results

The characteristics of the participants appear in Table 1. There was a statistically significant difference between the groups of people with schizophrenia with healthy control and male being the most participants. There was a statistically significant difference between age ($p < 0.001$) and BMI in the group of people with a control group of 23.94 ± 2.91 tested independent sample t-test obtained a score of $p < 0.001$ (there was a very significant difference in body mass index [BMI]).

Table 1: Demographic characteristics of people with schizophrenia and controls

Variable	Group		p-score
	Schizophrenic patients (n = 40)	Control (n = 40)	
Gender			
Male	28 70%)	23 (57.5%)	
Female	12 (30%)	17 (42.5%)	0.352*
Age	35.18 ± 2.87	29.93 ± 5.75	<0.001**
Education			
Junior high school	12 (30%)	3 (7.5%)	0.001***
Senior high school	21 (52.5%)	15 (37.5%)	
College	7 (17.5%)	22 (55%)	
Job			
Working	9 (22.5%)	20 (50%)	
Not working	31 (77.5%)	20 (50%)	0.020*
Wedding			
Married	6 (15%)	18 (45%)	
Unmarried	34 (85%)	22 (55%)	0.007*
Body mass index	21.77 ± 1.92	23.94 ± 2.91	<0.001**
Duration of sick	3 (1–5)	-	
PANSSa	99 (85–110)	-	

Categorical variables were presented with n (%), numeric variables with normal distribution were presented with mean±standard deviation, numeric variables with abnormal distribution were presented with the median score (minimum-maximum score). *Chi-square with continuity correction. **Independent-samples t-test. ***Pearson Chi-square test. Data are only for the group of people with schizophrenia.

The median duration of illness and total PANSS score is shown in Table 1.

In Table 2, median TNF-α levels in the group of people with schizophrenia were obtained at 3.40 with a minimum score of 0.65 and a maximum score of 43.8 while in the healthy control group, the median score of TNF-α was 14.75 with a minimum score of 5.18 and a maximum score of 31.1. The Mann–Whitney U-test was conducted because the data were not distributed normally and remained not distributed normally even

though log10 had been performed. Mann–Whitney U-test result got p < 0.001. Hence, it concluded that there were significant differences in TNF-α levels between groups of people with schizophrenia who received risperidone 4 mg in the acute phase of treatment and healthy control.

Table 2: Differences in TNF-α levels in people with schizophrenia who got risperidone 4 mg in the acute phase of treatment and healthy control

TNF-α	Median (Minimum-Maximum)	p-score
Schizophrenic patients	3.40 (0.65–43.8)	< 0.001
Healthy control	14.75 (5.18–31.1)	

*Mann–Whitney U-test ranked average people with schizophrenia at 31.38 and healthy control 49.63.
TNF: Tumor necrosis factor.

In Table 3, the average interleukin (IL)-2 level in people with schizophrenia was found to be 5.26 with a standard deviation of ±0.987 and at the controls at 3.43 with a standard deviation of ±0.665. In Table 3 to look for differences in IL-2 levels in the group of people with schizophrenia who received risperidone 4 mg in the acute phase of treatment and control, an independent test was conducted – sample t-test due to normally distributed data obtained p<0.001 results with a confidence interval of 1.44–2.19. Until the conclusion was drawn, there was a very significant difference in IL-2 levels between schizophrenic patients, which got risperidone 4 mg in the acute phase of treatment and control.

Table 3: Differences in IL-2 levels in people with schizophrenia who got risperidone 4 mg in the acute phase of treatment and healthy control

IL-2	Average ± SB	Average difference (95% IK)	p-score
Schizophrenic patients (n = 40)	5 0.26 ± 0.987	1.82 (1.44–2.19)	< 0.001
Healthy control (n = 40)	3.43 ± 0.665		

*Independent samples t-test. IL: Interleukin.

Discussion

Based on demographic characteristics in this study, males was the most groups of people with schizophrenia as well as healthy controls. There was no significant gender difference between the two groups. These results were by studies conducted by Tan and friends, in 2015 in Beijing (China) conducted a study to assess serum levels of IL-2 in a large group of 160 schizophrenic patients compared to 60 healthy control groups that from demographic data, there was no significant difference of gender between the group of schizophrenic patients and the healthy control group with p > 0.05 score, and conducted a two-way ANOVA test and found no significant difference between the genders (f = 0.05, df = 1.218, p = 0.82) [5].

In terms of age, group of people with schizophrenia presented with an average and standard deviation of age with 35.18± 2.87 years while the control group with an average and standard deviation of age with 29.93 ±5.75 years. This was according to Saddock *et al*., in 2015, in a book called schizophrenia spectrum and other psychotic disorder that peak age onset in male earlier than females. The peak onset of age in males are 10-25 years and 25-35 years in females [6].

On the demographic characteristics of marital status for the group of people with schizophrenia, married as many as six people (15 %) and unmarried 34 people (85%). Marital status for the group of control, married are 18 people (45%) and unmarried are 22 people(55%), with p=0.007. These results were in line with a study conducted by Pinho *et al*., in 2017, in Portugal, which said that people with unmarried schizophrenia were 190 people (67.4%), married 40 people (14.2%), and divorced 52 people (18.4%) [7].

In the demographic characteristics of educational status, group of people with schizophrenia with low education as many as 12 people (30%), middle education as many as 21 people (52.5%), highly education people as many as 7 people (17.5%). In the control group with low education subjects as many as 3 people (7.5%), middle education as many as 15 people (37.5%), highly education as many as 22 people (55%). This result was by the study of Huang *et al*. in Shanghai (China) in 2018 showing the highest level of high school education in people with schizophrenia is 39.5% (n = 43 people), junior high school 25.7% (n = 26 people), and college 34.8% (n = 38 people) [8].

On the demographic characteristics of employment status for the group of people with schizophrenia, the subject working as many as 9 people (22.5%) and did not working as many as 31 people (77.5 %). In the healthy control group with the subject working as many as 20 people (50 %) and did not working as many as 20 people (50%). These results were in line with a 2015 study by Bowmans and friends that found that people with chronic mental illnesses, including schizophrenia, were experiencing barriers to work due to stigma and discrimination [8],[9]. These results were in line with a 2015 study by Bowmans *et al*. that found that people with chronic mental illnesses, including schizophrenia, were experiencing barriers to work due to stigma and discrimination. Also in a 2017 study in Portugal about the social demographic influence on the quality of life of schizophrenia patients (9.2%) found data from 282 people with schizophrenia, who worked for just 26 people (9.2%) and the other 90.8% mentioned not working and unable to work [7], [9].

In demographic characteristics of body mass index (BMI) for the group of people with schizophrenia, an average and standard deviation of body mass index are 35.18±2.87 and the healthy control group are 23.94±2.91. According to a study conducted by Juncal-Ruiz *et al*., in 2018 in Spain, in this study, it was concluded that being overweight can alter the homeostasis of the immune system. It can, therefore, cause pro-inflammatory additive effects caused by psychosis in the CNS [10].

In this study, the differences in TNF-α levels in people with schizophrenia who got the drug therapy of risperidone with 4mg per day in the acute phase of treatment and healthy control with the number of subjects are 40 people each group. Median TNF levels – α in the group of people with schizophrenia obtained 3.040 with a minimum score of 0.65 and a maximum score of 43.8 while in the healthy control group the median score of TNF – α is 14.75 with a minimum score of 5.18 and a maximum score of 31.1. These results are in line with a study conducted by Han *et al*. in 2014 in Beijing (China) conducted a clinical study that assessed TNF-α levels in schizophrenia as many as 89 people and a control group of 43 people who showed very significant differences in TNF-α levels between the group of people with schizophrenia and control group ($p < 0.01$) [2].

In this study, the difference in IL-2 levels in people with schizophrenia who received risperidone 4 mg in the acute phase of treatment and healthy control with 40 subjects was 5.26 with a standard deviation of ±0.987 and at healthy control at 3.43 with a standard deviation of ±0.665. These results were in line with a study conducted by Zhang *et al*. in 2002 in Beijing (China) conducted a clinical study that assessed IL-2 levels in people with schizophrenia as many as 67 people and a control group of 26 people showed a significant difference that IL-2 levels in people with schizophrenia were higher than in the control group [11].

The results differed from a study conducted by Asevedo *et al*. in 2014 in Brazil conducted a case–control study to determine the correlation of IL-2 levels in peripherals with negative and cognitive symptoms. The study was conducted in a group of 29 people with schizophrenia and a control group of 26. The results of this study found significant differences in IL-2 levels between the groups of people with schizophrenia and the control group ($p < 0.001$). Differences from studies conducted by Asavedo *et al*. were that people with schizophrenia had lower IL-2 levels compared to the control group while in this study found higher levels of IL-2 in the group of people with schizophrenia compared to the control group. This, according to studies conducted by Tan *et al*., can occur due to several factors such as differences in measuring IL-2 levels, material differences tested (serum or plasma), or length of blood sample storage period, blood samples were taken from people with schizophrenia with different phases of disease (active phase or remission phase), exposure to other groups, doses, and length of use of anti-psychotics or biological heterogeneity may affect the difference in these results [5].

IL-2 is a pro-inflammatory cytokine that activates cellular immunity and plays a key role in the effective immune response to pathogens. IL-2 has released blood circulation from CD-4 + activated T cells and usually appears blooded at low levels. Increased IL-2 levels indicated activation of the immune system. The T-cell exhaustion theory proposes that *in vitro* decreasing IL-2 production is a consequence of *in vivo* overproduction of IL-2, which meant that activated T cells and IL-2 derived from lymphocytes had been released into the blood serum. Further, the macrophages T lymphocyte theory proposed that IL-1, IL-2, TNF-α, interferon-α, and interferon-γ produced by chronically activated macrophages and T lymphocytes were fundamental mediators of schizophrenia [5].

Conclusions

There is a significant difference in TNF-α levels between groups of people with schizophrenia who get risperidone 4 mg in the acute phase of treatment and control. There was a significant difference between IL-2 levels between people with schizophrenia who got risperidone 4 mg in the acute phase of treatment and control.

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