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INTERLEUKIN-18 LEVELS IN SCHIZOPHRENIA PATIENTS RECEIVING ANTI-PSYCHOTIC THERAPY AT THE PSYCHIATRIC POLYCLINIC OF SITI RAHMAH ISLAMIC HOSPITAL

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ABSTRAK

Penggunaan terapi antipsikotik efektif dalam mengatasi gejala dan telah menjadi pilar pengobatan utama pada pasien skizofrenia. Namun, antipsikotik berefek samping terhadap sitem imun, terutama kadar Interleukin 18 (IL-18). Maka dari itu, penting untuk mengetahui kadar IL-18 pada pasien skizofrenia yang mendapat antipsikotik.Tujuan: mengetahui kadar IL-18 pada pasien skizofrenia yang mendapatkan terapi antipsikotik dan menjalani pengobatan rawat jalan di poliklinik RSI Siti Rahmah Padang. Metode penelitian deskriptif ini merekrut 25 pasien skizofrenia yang mendapat pengobatan antipsikotik yang dengan sukarela ikut serta. Pemeriksaan IL-18 dilakukan dengan metode ELISA dari serum pasien. Hasil pada 25 pasien skizofrenia sebanyak yang mendapatkan terapi antipsikotik diperoleh kadar IL 18 sebanyak 483,7 ± 27,3 ng/ml, paling banyak ditemukan pada penelitian ini yaitu 60% pada usia 36-45 tahun, 88% pada pasien laki-laki, 64% pasien menggunakan antipsikotik atipikal. Kesimpulan penelitian ini menunjukkan kadar IL-18 pada pasien skizofrenia yang mendapatkan antipsikotik di RSI Siti Rahmah Padang didapatkan tinggi.

ABSTRACT

Interleukin-18 Levels in Schizophrenia Patients Receiving Anti-Psychotic Therapy At The Psychiatric Polyclinic Of Siti Rahmah Islamic Hospital. The use of antipsychotic therapy is effective in managing symptoms and has become a cornerstone in the treatment of patients with schizophrenia. However, antipsychotics have side effects on the immune system, particularly affecting Interleukin 18 (IL-18) levels. Therefore, it is important to assess IL-18 levels in schizophrenic patients receiving antipsychotic therapy. Objective: To determine IL-18 levels in schizophrenic patients undergoing antipsychotic therapy and receiving outpatient care at the RSI Siti Rahmah Padang clinic. This descriptive study recruited 25 schizophrenic patients receiving antipsychotic therapy who voluntarily participated. IL-18 levels were measured using the ELISA method from patient serum. Results: In 25 schizophrenia patients who received antipsychotic therapy, IL 18 levels were obtained as much as 483.7 SD ± 27.3 ng/ml. The subjects were aged 36-45 years (60%), 88% were male, and 64% were using atypical antipsychotics. Schizophrenic patients receiving antipsychotic therapy at RSI Siti Rahmah Padang showed elevated IL-18 levels.

INTRODUCTION

Schizophrenia comes from the Greek word *schizo* and *phrenos*. *Schizo* means split, and *phrenos* means mind. Schizophrenia in the language is a split mind. Schizophrenia is defined as a thought disorder accompanied by hallucinations and delusions .[1] schizophrenia occurs due to an imbalance of neurotransmitters in the form of hypersecretion of dopamine, serotonin, glutamate, and GABA (*gamma-aminobutyric acid*).[1,2] The increase in schizophrenia cases is occurring both globally and nationally .[2]

World Health Organization) data from 2018 stated that 24 million people, or 1 in 300 people worldwide, suffer from schizophrenia.[3] The incidence of schizophrenia globally in men (0.6 million cases) is higher than in women (0.54 million cases). The age group with the highest prevalence of schizophrenia is 20-29 years old. [4] The prevalence of schizophrenia in East Asia reaches 8 million, South Asia 4 million, and Southeast Asia 2 million. [5] China has the highest prevalence of schizophrenia in Asia, namely 7.8 million people who have schizophrenia.[6] The increase in the prevalence of schizophrenia in China was recorded at 0.39% (3.09 million) in 1990, 0.57% in 2000, 0.83% (7.16 million) in 2010, and in 2020 reached 7.8 million cases. [6,7] The prevalence of schizophrenia in Southeast Asia ranks third highest in the Asian region. This factor is related to many developing countries in the Southeast Asian region, except Singapore.[8]

The Health Research and Development Agency (Balitbangkes) of the Indonesian Ministry of Health in 2018 showed that the prevalence of schizophrenia in Indonesia was 7.0 per mil. [9] The highest distribution was in Bali at 11.1 per mil, and West Sumatra was ranked 4th after NTB with research results of 9.1 per mil. [10,11] The most common cases in West Sumatra were found in the mental hospital. Prof. HB Saanin Padang. Profile data from the Mental Hospital Prof. HB Saanin Padang in 2018 showed that the number of patients in the polyclinic was 11,715, with schizophrenia patients as many as 9,480 patients or 80.92% of the total profile data.[12]

The cause of schizophrenia is generally idiopathic, but schizophrenia is caused by certain factors, namely internal and external factors. Internal factors come from genetics, biochemistry, and neuropathology. External factors can come from psycho-social and the surrounding environment, including excessive stress.[1,13] schizophrenia consists of 3 symptoms. The first symptoms are hallucinations and delusions, which are positive symptoms.[1] The second symptom is negative symptoms such as loss of interest and motivation towards something.[14] The third symptom is a symptom of cognitive decline in the form of being easily distracted by something.[15] One of the therapies used to treat the symptoms of schizophrenia is antipsychotics.[1]

Antipsychotics are a therapy for schizophrenia patients that works by inhibiting D2 and 5HT2A receptors. 1 In general, antipsychotics are divided into two types, namely first-generation antipsychotics (dopamine receptor antagonists) and second-generation antipsychotics (serotonin dopamine antagonists).[16] Schizophrenia patients experience increased IL-18 due to neurotransmitter imbalance, which causes stress abnormalities. IL-18 mediates stress in the *kynurenine pathway* involved in neurotransmission. This causes IL-18 to increase in serum. [17,18] Antipsychotic therapy can also increase IL-18 through histamine one blockade so that appetite increases. IL-18 works by inhibiting the activity of the transcription factor, namely *nuclear factor kappa* (NF-kB). *Nuclear factor kappa* (NF-kB) functions as a regulator of proinflammatory gene expression, especially IL-18. IL-18 predicts increased total cholesterol and LDL as a potential

occurrence of metabolic syndrome.[17] *American Heart Association* study stated that 43% of schizophrenia patients have metabolic syndrome and an increased risk of death related to metabolic syndrome. This study stated that there was an increase in total cholesterol, triglycerides, LDL (*Low-Density Lipoprotein*), VLDL (*Very Low-Density Lipoprotein*), and a significant decrease in HDL (*High-Density Lipoprotein*). MRI examination proved that there was an increase in subcutaneous intra-abdominal fat in schizophrenia patients due to Second Generation Antipsychotics (IIAPG).[19] Based on the explanation above, this study aims to determine the levels of IL-18 in schizophrenia patients receiving antipsychotic therapy at Prof. Hb Saanin Mental Hospital, Padang.

METHOD

The study was conducted at the Siti Rahmah Islamic Hospital in Padang from July to September 2024 by recruiting 25 patients who had been diagnosed with schizophrenia by a psychiatrist based on DSM V and who met the inclusion criteria, namely being over 17 years old who received antipsychotic therapy for at least 3 months and were willing to have blood drawn and sign *an informed consent.* Exclusion criteria were schizophrenia patients who were uncooperative and unable to communicate well. This research was conducted at the Biomedical Laboratory of the Faculty of Medicine, Baiturrahmah, and has passed the ethical review test at the Faculty of Medicine, Baiturrahmah University with ethical number 019/ETIK-FKUNBRAH/03/09/2024. Data was presented using descriptive analysis, with categorical data shown as frequency and percentage and numerical data expressed as mean and standard deviation.

RESULTS

This descriptive study recruited 25 schizophrenia patients receiving antipsychotic medication who volunteered to participate. IL-18 examination using the ELISA method from patient serum. The results of the study of data collection and analysis obtained, following table:

Table 1. Frequency Distribution of Respondents

Variables	F	%
Age		
17-25 Years	2	8, 0
26-35 Years	3	1 2, 0
36-45 Years	15	60.0
46-55 Years	5	2 0.0
56-65 Years	0	0
> 65 Years	0	0
Gender		
Man	22	8 8.0
Woman	3	12.0
Types of Antipsychotics		
APG I	1	4.0
APG II	16	64.0
Combination	8	32.0
IL-18 levels	483.7 ± 27.3 ng/ml,	
Total	**25**	**100.0**

DISCUSSION

This study shows the frequency distribution of respondents based on age obtained from 40 samples, showing that most of the 52.5% were aged 36-45 years. This is supported by research by Marco *et al.,* stating that the most schizophrenia patients globally in 2021 were in the 25-49 year age range, with a percentage of 47.8%.[20] Another study by Rony *et al.* at the psychiatric polyclinic of the Lampung Regional Mental Hospital in 2023 stated that most cases of schizophrenia occurred in the 36-45 year age range, namely 32.17%.[21]

Schizophrenia cases in the 36-45 age range are theoretically caused by various factors, namely genetic, psychological, and environmental factors. The interaction of genetic factors can increase the risk of schizophrenia at the individual level. The age of 36-45 years is identified as a period in which genetic factors have a more significant impact. Psychological factors, such as stress and life pressures, can trigger or worsen symptoms of schizophrenia. This age range is often a challenging and stressful period of life, which contributes to the development of schizophrenia. Environmental factors, both socially and in everyday life, also play an important role in the onset of schizophrenia. These factors significantly influence individuals aged 36-45 years, where life pressures and social responsibilities peak.[21]

It is important to remember that schizophrenia is multifactorial, and the complex interactions between genetic, psychological, and environmental factors are still an area of active research. If someone is experiencing symptoms that could be related to schizophrenia at any age, consulting a mental health professional can provide a thorough evaluation and guidance regarding appropriate diagnosis and treatment.[1]

Another factor that can influence schizophrenia, which often occurs between the ages of 36-45 years, is the existence of life pressure, psycho-social, environment/lifestyle, type of work, education level, income-expenditure level, and stress level are risk factors for schizophrenia. [22] Therefore, those aged 36-45 years tend to be more susceptible to schizophrenia.

This study shows the frequency distribution of respondents based on gender obtained from 40 samples, showing that most of them, 87.5%, were male. In line with research at the Dr. Arif Zainuddin Surakarta Regional Mental Hospital, it was stated that men dominated schizophrenia patients by 80%. [23] This study has the same results at the Lampung Regional Mental Hospital, namely that most schizophrenia patients were men, 71 people (61.74%) and women, 44 people (38.26%).[21]

The results of gender differences in the cause of schizophrenia are more common in men because men tend to withdraw and do social isolation when stressed, have low self-care, and it is tough to express emotions than women when stressed. The consequences that arise from this cause men to have a higher risk of adverse symptoms than women. The stress pressure experienced by men has a higher risk of developing negative symptoms and disorganization.[6]

Schizophrenia cases mainly occur in men and theoretically can be triggered by testosterone to psychotic disorders. *Dehydroepiandrosterone* (DHEA) and its metabolite (DHEA *sulfate* [DHEA-S]) are precursors of adrenal steroids in testosterone synthesis. Testosterone and DHEA are known to affect the dopaminergic and glutamatergic neurotransmission systems, which are believed to cause neurotransmitter imbalances related to the pathophysiology of schizophrenia. The three neuroactive steroids (DHEA, DHEA-S, and testosterone) have several implications for the occurrence of schizophrenia.[24]

The impact causes the cognitive, emotional, social, or adaptive functions of men to be worse. It causes the morphology of the male brain to show many abnormalities in the form of enlarged ventricles and atrophy of the frontal lobe, hippocampus, amygdala, and temporal. [25] The abnormality of the brain morphology has an impact on dopaminergic activity in men so that men express stressors excessively and uncontrolled emotions.

Another theory states that women are not susceptible to schizophrenia because they have the hormone estrogen, which can be a protective factor for women. The hormone estrogen has an antipsychotic effect; namely, it can maintain the balance of neurotransmitters, and estrogen can protect women from brain morphological abnormalities.[26]

Other factors that cause schizophrenia cases dominated by men, apart from hormonal factors, can be caused by specific risk factors, such as low education levels, unemployment, and unmarried marital status, as well as poor stress management, which can increase the risk of schizophrenia.[27]

This study shows the frequency distribution of respondents based on antipsychotic therapy obtained from 40 samples, showing that most of them, 52.5%, consumed APG II. In line with the research at the Siti Rahmah Padang Islamic Hospital, schizophrenia patients mostly consumed the second-generation antipsychotic type (APG II), namely 32 people (64%).[28]

Another study at the Sungai Bangkong Pontianak Regional Mental Hospital found that the type of antipsychotic therapy for schizophrenia patients mainly was APG II, with as many as 66 people (72.19%). [29] Schizophrenia research at the Bali Provincial Mental Hospital in 2019 stated that schizophrenia patients in the hospital mostly consumed APG II type antipsychotics, as many as 57 people (58.2%).[30]

The use of APG II is more widely used in schizophrenia patients because it can improve the symptoms of schizophrenia and is more effective. Second-generation antipsychotics (APG II) are known to have good efficacy in reducing positive symptoms (such as hallucinations and delusions) and negative symptoms (such as apathy and social withdrawal) in schizophrenia.

Second Generation Antipsychotics (IIAGs) affect serotonin receptors, particularly 5-HT2A. Effects on serotonin may provide additional benefits in treating symptoms of schizophrenia and *mood disorders.*[31] Second-generation antipsychotics tend to have lower effects on the autonomic nervous system, which contributes to reduced side effects such as orthostatic hypotension compared to APG I. As a result, APG II has a lower frequency of side effects of abnormal movements and motor disorders than APG I. This can also increase the level of patient compliance with antipsychotic therapy. [32] In contrast to APG I, which is less effective in overcoming negative symptoms in schizophrenia patients, the extrapyramidal effects caused are very high.[1,30]

First Generation Antipsychotics (GPA I) theoretically work by inhibiting D2 (dopamine) receptors in the limbic system in the brain. First Generation Antipsychotics (GPA I) have side effects of extrapyramidal syndrome and neuroleptic malignant syndrome. These side effects of GPA I make GPA II an antipsychotic that is given to schizophrenia patients because of its minor extrapyramidal effects.[1] This is what makes APG II the dominant choice in treating the complex spectrum of symptoms in schizophrenia with side effects that are not as severe as APG I.

This study shows the frequency distribution of respondents based on IL-18 levels obtained from 25 samples, showing that the average IL-18 levels in the schizophrenia patient group were higher when compared to the control group in other literature. The increase in IL-18 to high levels

in schizophrenia with APG II therapy compared to *non*-schizophrenia with normal IL-18 levels. [33] An increase in IL-18 to high levels in schizophrenia patients due to APG I therapy compared to *non*-schizophrenia with normal IL-18 levels.[34]

IL-18 is a proinflammatory cytokine that plays a significant role in the pathophysiology of metabolic syndrome. This condition often occurs in patients with schizophrenia who are on long-term antipsychotic therapy. IL-18 is involved in regulating energy metabolism and the systemic inflammatory response, where high levels can trigger metabolic dysfunction. Studies have shown that IL-18 increases macrophage activity and produces other proinflammatory cytokines, such as TNF-α and IL-6, contributing to insulin resistance, obesity, and dyslipidemia. Activating these inflammatory pathways can also worsen metabolic processes by inducing oxidative stress and increasing lipid accumulation in adipose tissue and the liver, which are characteristics of metabolic syndrome. In patients with schizophrenia, high levels of IL-18 often correlate with metabolic side effects of antipsychotics, especially second-generation (atypical) antipsychotics, which are known to worsen insulin resistance and increase the risk of metabolic syndrome.

In addition, high levels of IL-18 in schizophrenia patients may reflect a complex interaction between chronic inflammation and metabolic dysfunction. This cytokine plays a role in the inflammasome pathway, especially the NLRP3 inflammasome activated in patients with insulin resistance and obesity. This inflammasome stimulates IL-18 secretion, further exacerbating chronic inflammation, increasing free fatty acid release, and inhibiting glucose uptake by skeletal muscle. These mechanisms not only increase the risk of metabolic syndrome but also lead to long-term metabolic complications, including type 2 diabetes mellitus and cardiovascular disease. Therefore, IL-18 plays a key mediator linking chronic inflammation to metabolic syndrome in schizophrenia patients, making it a potential biomarker for monitoring metabolic side effects of antipsychotic therapy and identifying patients who require additional intervention to prevent metabolic complications.

The increase in IL-18 is an immune response to changes in neurochemical or neuroinflammatory levels associated with schizophrenia or antipsychotic treatment. Interleukin 6 is a proinflammatory cytokine in the immune response produced in various cells and the brain by astrocytes and microglial cells. IL-18 controls body weight, food intake, and energy expenditure by stimulating the *hypothalamic-pituitary-adrenocortical* (HPA) axis. Interleukins affect catecholamine neurotransmission, especially dopaminergic and serotoninergic pathways in the hippocampus and frontal cortex.[18]

Antipsychotics, especially APG I, have effects on the central nervous system, especially on dopamine receptors in the brain. Changes in dopamine neurotransmission can affect immune responses and cytokines such as IL-18.[35.] First-generation antipsychotics can also affect the endocrine system and hormone release, thereby affecting the immune response and inflammation. [36] This will trigger the production and release of proinflammatory cytokines such as IL-18. IL-18 levels due to APG I become high in serum through this mechanism.[33]

Second-generation antipsychotics also have effects that can increase IL-18. APG II's action mechanism in inhibiting histamine (H1) and serotonin 5HT2C can result in increased food intake. IL-18 also influences catecholaminergic neurotransmission in the dopaminergic and serotoninergic pathways. The effect of APG II will cause IL-18 to increase in metabolism due to excessive food intake so that in metabolic tissue (adipose tissue, pancreatic islets, liver, muscle, and brain), there will be

an increase in adipose tissue, insulin sensitivity, and blood pressure. [37]This effect results in high IL-18 levels due to APG II and a high risk of *Metabolic Syndrome* (MetS) due to APG II.[18]

Several other factors can affect the results of high IL-18 levels besides antipsychotics, namely genetic variants of a person's index period, environmental factors, socio-economic factors, and lifestyles. The type of antipsychotic used can affect the impact on IL-18 levels. This study requires further research to see whether the increase in IL-18 is related to APG I, APG II, or a combination.

This study has limitations in sample size and the singular site of its execution, which may hinder the generalizability of the results to the broader schizophrenia population, particularly beyond the geographic and demographic setting of the study. This study also failed to precisely account for factors such as the duration of antipsychotic therapy, dosage variations, or other comorbidities that could influence IL-18 levels. These elements may serve as confounding variables that influence the study's outcomes.

CONCLUSION

This study concludes that interleukin 18 levels are high in schizophrenia patients during antipsychotic treatment.

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