CORRELATION BETWEEN GLUTATHIONE (GSH) LEVELS AND COGNITIVE FUNCTION IN PEOPLE WITH SCHIZOPHRENIA

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Abstract.

Background: Cognitive impairment is a prevalent manifestation observed in people with schizophrenia and holds significant value in predicting the clinical and functional prognosis of the disease. Even though cognitive deficits are not the primary diagnostic criterion for schizophrenia, they can exacerbate the condition of patients and negatively impact their quality of life. A reduced concentration of glutathione (GSH) has been linked to this impairment in healthy individuals and numerous other neuropsychiatric conditions, such as Alzheimer's and Parkinson's disease. This study investigates whether a correlation exists between GSH levels and cognitive function in people with schizophrenia. It contributes to a better comprehension of the pathophysiology of schizophrenia and facilitates the development of more efficacious treatment strategies for cognitive impairment associated with this disease.

Method: This is a correlational analytic study with a cross-sectional approach, which assesses the correlation between GSH levels and cognitive function in people with schizophrenia. The sampling technique employed in this study is non-probability consecutive sampling. This method involves including all individuals who meet the predetermined selection criteria until the desired sample size is achieved. For this study, a total of 65 individuals were included, consisting of 43 males and 22 females.

Results: In this study, the male population accounted for the majority, comprising 66.15% of the total sample. The highest level of education attained by the participants was senior high school, with a prevalence of 75.38%, and the most frequently reported marital status was unmarried, at a proportion of 72.30%. Furthermore, 72.30% reported being unemployed, and regarding ethnic background, the Batak population had the highest representation, accounting for 78.46%. The median age of people with schizophrenia, PANSS, and median duration of illness was 34 years (range of 20-40 years), 65 (score range of 60-73), and four years (duration range of 2-10 years), respectively. The median GSH level in the study subjects was 9.00 µg/ml. Furthermore, there was a significant strong positive correlation ($p < 0.001$) between GSH levels and cognitive function in people with schizophrenia. This indicated a relationship between GSH levels and MoCA-Ina scores (cognitive function).

Conclusion: This study found a correlation between GSH and cognitive function, where the two variables are directly proportional.

Keywords : glutathione, cognitive function, schizophrenia

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Introduction

Schizophrenia is a challenging mental disorder characterized by its severity, persistence, and episodic nature. It typically progresses through distinct phases over time. The acute phase is marked by positive symptoms like delusions and hallucinations, while the chronic phase is associated with negative symptoms, cognitive deficits, and impaired social functioning [1],[2]. This mental disorder affects around 24 million people or 1 in 300 (0.32%) on a global scale. Schizophrenia typically manifests during late adolescence and early adulthood, with males experiencing an earlier onset than females [3]. It is multifaceted and heterogeneous, attributed to diverse biological pathways of causation. Despite this complexity, oxidative stress (OS) is the underlying factor that links these various pathways. It remains unclear whether OS is the primary cause of the disease or occurs as a secondary effect under the influence of environmental factors or prolonged medication use. However, there is a consensus that OS plays a crucial role in the pathogenesis of schizophrenia [4]. Glutathione (GSH) is the primary antioxidant in the brain and vital for maintaining oxidative balance. OS can occur when the balance between Reactive Oxygen Species (ROS) and antioxidant defence is disrupted, resulting in cell toxicity and damage. In addition, abnormal levels of dopamine and glutamate release, as implicated in schizophrenia and bipolar disorder, can lead to neural OS, which can be exacerbated by GSH deficiency [5].

People with schizophrenia often experience a deficit in GSH levels, disrupting normal myelination and leading to clinical symptoms, including cognitive impairment. Previous Clinical studies established a positive correlation between GSH levels in the medial prefrontal cortex and the integrity of white matter in the cingulum bundle of patients with early psychosis. Despite recognizing increased OS and reduced GSH levels as contributing factors in schizophrenia, the relationship between GSH levels and the severity of clinical symptoms and brain function remains unclear. Some studies showed a correlation between lower GSH levels and more severe clinical signs, including cognitive dysfunction [6]. Therefore, this study aims to determine the correlation between GSH levels and cognitive function in people with schizophrenia in Indonesia.

Methods and results

Methods

This correlational analytical study uses a cross-sectional approach, which assesses the correlation between GSH levels and cognitive function in people with schizophrenia. The sampling method used is non-probability consecutive sampling. The sample size for this study is 65 individuals (43 males and 22 females), conducted at Dr Pirngadi Regional General Hospital Medan from September 2022 to May 2023. Glutathione levels examination was performed at the Integrated Research Laboratory Faculty of Medicine Sumatera Utara University. The inclusion criteria for this study were people with schizophrenia aged 20 to 40 who have been treated for at least two years with atypical antipsychotics, with PANSS scores between 60 and 80. After obtaining written consent from samples, the subject demographics data were collected, and blood samples were taken and examined using the ELISA method to determine the in vitro quantitative concentration of GSH in plasma, and MoCA-Ina scores were calculated. Correlation between GSH levels and MoCA-Ina scores was performed using the Spearman test.

Results

In this study, the male population accounted for the majority, comprising 66.15% of the total sample. The highest level of education attained by the participants was senior high school, with a prevalence of 75.38%, and the most frequently reported marital status was unmarried, at 72.30%. Furthermore, 72.30% reported being unemployed, and regarding ethnic background, the Batak population had the highest representation, accounting for 78.46%. The median age of people with schizophrenia was 34, with the youngest and oldest being 20 and 40 years old. The median PANSS score was 65, with the lowest and highest scores being 60 and 73, and the median duration of illness was 4 with a minimum and maximum value of 2 and 10 years, as shown in Table 1.

The median value of GSH levels was 9.00 μg/ml, with the lowest and highest at 3.40 and 18.10, respectively, as shown in Table 2. The median score of MoCA-Ina was 24, with minimum and maximum scores of 21 and 27, respectively, as shown in

Table 3. There was a significant correlation between GSH levels and cognitive function in people with schizophrenia, with a p-value of <0.001 and a Spearman coefficient of +0.630, indicating a strong positive correlation. Therefore, GSH levels are directly proportional to the MoCA-Ina score (cognitive function) in people with schizophrenia, as shown in Table 4.

Table 1 Distribution of study subjects based on demographic characteristics

Demographics Characteristics	Median (min-max)	n	(%)
Gender			
Male		43	66,15
Female		22	33,85
Level of education			
Junior High School		16	24,62
Senior High School		49	75,38
Marital status			
Married		18	27,70
Unmarried		47	72,30
Employment			
Work		18	27,70
Unemployed		47	72,30
Ethnic group			
Batak		51	78,46
Java		8	12,30
Malay		4	6,17
Other		2	3,07
Age	34 (20 – 40)		
Long Sick	4 (2 – 10)		
PANSS score	65 (60 – 73)		

Table 2. GSH levels in people with schizophrenia

	n	Median (minimum-maximum) (µg/ml)
GSH levels	65	9,00 (3,40 – 18,10)

Table 3. MoCA-Ina scores in people with schizophrenia

	N	Median (minimum-maximum)
MoCA-Ina score	65	24 (21-27)

Table 4. Results of analysis of the Spearman correlation test between GSH levels and cognitive function of people with schizophrenia

	Cognitive Function
GSH levels	r = +0,630
	p <0,001
	n = 65

Discussion

This study also shows more male participants than females, which aligns with previous findings indicating a higher prevalence of male samples in studies related to people with schizophrenia [7,8,9]. Schizophrenia affects approximately 24 million people or 1 in 300 (0.32%) worldwide. It typically develops during late adolescence and early adulthood, and often occurs earlier in males than females [3]. This current study reports a median age of 34 years for the subjects aged 20 to 40. In Indonesia, the highest prevalence of the disorder was observed among individuals aged 30-34 and 25-29, with no apparent gender-based differences [10].

This study found a median value of GSH levels in people with schizophrenia of 9.00 µg/ml with minimum and maximum values of 3.40 and 18.10 µg/ml. Several studies showed that people with schizophrenia tended to have lower glutathione levels

than healthy individuals, specifically in patients subjected to antipsychotic therapy [11]-[14]. This is related to the lipophilic nature of antipsychotic drugs that can enter cell membranes and disrupt neuronal metabolism, causing an imbalance in free radical processes. The reduction in GSH concentration appears to be related to pathogenesis and dependent on decreased synthesis capacity [15].

This study reported that MoCA was a good screening instrument to assess cognitive impairment in schizophrenia. Several studies suggested using different cut-off points on MoCA to detect cognitive impairment, including a cut-off point of <25 in psychotic patients and 26 to detect cognitive dysfunction in MoCA-Ina. An American study found that the mean MoCA score in people with schizophrenia was 20.17 ± 4.19, significantly lower than healthy controls. In a separate study conducted in Singapore, the MoCA was a reliable tool for assessing moderate to severe cognitive dysfunction, with <25 and <23 cut-off scores, respectively [16]-[18].

This study highlighted a correlation between GSH levels and cognitive function in people with schizophrenia and did not measure GSH levels in healthy controls. Specifically, the findings indicated that lower GSH levels were associated with lower cognitive function scores. Even though cognitive deficits were not considered a primary diagnostic feature of schizophrenia, they were commonly observed in patients and significantly predicted clinical and functional outcomes. Studies suggested that peripheral GSH levels might have served as a predictive marker for these patients' brain function and clinical outcomes. However, further investigation was required to elucidate the relationship between these variables in schizophrenia fully. Abnormal levels of dopamine and glutamate release, which were implicated in schizophrenia, could lead to neuronal OS, resulting in reduced GSH levels and impaired cognitive function [5],[19].

Conclusion

In conclusion, there is a correlation between GSH levels and cognitive function in people with schizophrenia. Even though cognitive deficits are not the main diagnostic feature of schizophrenia, the impairment is often found in patients and is a critical predictor of clinical and functional prognosis. Furthermore, peripheral GSH levels may serve as a predictive marker for brain function and clinical outcomes in people with schizophrenia. The relationship between these variables in people with schizophrenia needs further investigation. The reduction in GSH levels can affect cognitive function because abnormal levels of dopamine and glutamate release can cause neuronal OS exacerbated by GSH deficiency.

Ethics Approval and Consent to Participate

This study was approved by the Research Ethics Committee at the Faculty of Medicine, the University of North Sumatra (USU), with the letter number 1170/KEP/USU/2022 on November 29, 2022. All participants had written and signed their consent to participate.

Transparency Declaration. Competing interests: None to declare.

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