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Correlation of Serum Vitamin D Levels with Cognitive Function in Schizophrenic Patients

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Abstract

Introduction: Mental health problems, like schizophrenia, have been very prevalent in the 21st century. Over the year, especially during the coronavirus disease 2019 pandemic, its cases have been continuously increasing. The pandemic also keeps people from going outside, preventing them from getting enough sunlight exposure. This results in low level of Vitamin D. Interestingly, several studies also have shown that patients with schizophrenia generally have low Vitamin D. Other studies have also found that Vitamin D could have a significant role on the pathophysiology of schizophrenia. This study aimed to determine the correlation between Vitamin D level and cognitive function of schizophrenic patient.

Material and Methods: The study was conducted at Dr. Amino Gondohutomo Regional Psychiatric Hospital. It was conducted with a cross-sectional method. Schizophrenic patients that fulfilled the inclusion and exclusion criteria were selected with consecutive sampling method. The patient then underwent cognitive test with Montreal Cognitive Assessment-Indonesia questionnaire to assess their cognitive function and blood work to determine their Vitamin D level.

Results: Of the 18 respondents who were selected as research subjects, the average score of cognitive function was at a low level of 15.72 out of 30. Compared with other domains, memory domain has the lowest average score. The average Vitamin D level was also deficient at only 16.3 ng/dL.

Conclusions: The correlation between Vitamin D level and cognitive function of patient with schizophrenia is significant (p=0.039). The correlation is positive with moderate strength (r=0.49).

Key words: Schizophrenia • Montreal Cognitive Assessment • Cognitive function • Vitamin D • Sun Exposure

Introduction

Schizophrenia is a syndrome with a wide variety of causes and course. It is a disease that affects both human behavior and mental function. Schizophrenia is a major problem that is increasing over time. There are several symptoms that arise in schizophrenic patients, and each patient has their own uniqueness, namely, positive symptoms (delusions and hallucinations), negative symptoms (apathy, infrequent speech, and blunted emotional responses), cognitive dysfunction that can interfere with social and work functions, motor disorders (catatonic behavior), and behavioral disorders [1].

In 2008, the global prevalence of schizophrenia ranged from 0.18% to 1.16%. According to Indonesia Basic Health Research (RISKESDAS), the household prevalence of schizophrenia is 6.7 per mil household in Indonesia alone. These numbers are also predicted to increase with the coronavirus disease 2019 (COVID-19) pandemic as a result of the stress of traveling during the pandemic and the fear of having close contacts infected with COVID-19 [2,3]. However, according to World Health Organization (WHO) data, Indonesia is ranked first in the world for disability-adjusted life years, with 321,870 [4].

One theory that explains the cause and course of the emergence of schizophrenia symptoms is an increase in dopamine activity along with a decrease in glutamatergic activity [5]. The decrease in activity of glutamate is due to the attachment of a receptor antagonist to the glutamatereceptor, namely, the N-methyl-D-aspartate (NMDA) receptor. This NMDA receptor antagonist is kynurenic acid. Kynurenic acid is a product of tryptophan metabolism, and its production is increased when there is a type 2 immune response, which is a pro-inflammatory immune response. With the blocking of this glutamatergic pathway, symptoms begin to appear, especially cognitive dysfunction because the glutamatergic pathway regulates many human cognitive domains [6-9].

Vitamin D deficiency has been associated to a higher risk of mental health problems and a negative response to stress. Risk factors associated with Vitamin D deficiency include obesity, dark skin tone, living in a country with low sun exposure, gastrointestinal malabsorption, renal insufficiency, liver disease, and wearing closed clothing and sunscreen [10]. About 50% to 90% of Vitamin D in humans is produced through the skin using energy from sunlight while the rest comes from nutritional intake. Lack of sun exposure is widely observed, especially during this pandemic, where some of the activity that was originally performed outside the house or building has moved inside. Reduced sun exposure reduces Vitamin D biosynthesis in the skin. This is a strong factor in the pathophysiology of Vitamin D deficiency because studies have shown that sun exposure can increase Vitamin D synthesis [11].

Previous studies have shown that compared with healthy individuals, patients with schizophrenia have lower levels of Vitamin D. In a study conducted in Cairo, Egypt, it was discovered that 80% of patients with schizophrenia had serum Vitamin D levels below normal [12]. In addition, only 1 in 90 schizophrenia patients studied in a mental hospital in Nigeria had normal serum Vitamin D levels [13].

It has been established that people with schizophrenia do experience a decrease in their Vitamin D levels. In addition, it is known that Vitamin

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D helps to reduce inflammation, and that inflammation contributes to the pathophysiology of schizophrenia. However, some studies suggest that low levels of Vitamin D have no effect on the overall severity of schizophrenia symptoms experienced by patients [13,14]. The difference in results with this theory has attracted researchers to conduct more in-depth research on the correlation between Vitamin D and symptoms of cognitive function in schizophrenic patients. This study hypothesize that there is a significant positive correlation between Vitamin D level and cognitive function in schizophrenic patients.

Materials and Methods

Study design and data source

This study is an analytical observational study with cross-sectional method. This study was conducted on schizophrenic patients at the Dr. Amino Gondohutomo Regional Psychiatric Hospital. Patients' data was collected using Montreal Cognitive Assessment-Indonesia (MoCA- Ina) questionnaire and taking blood serum for Vitamin D examination; both of which was carried at the mentioned hospital. Data collection took place from late June to early July 2022.

Study object and case definition

The samples used in this study were 18 patients diagnosed with schizophrenia who met the inclusion and exclusion criteria, with the selection of samples through consecutive sampling. The inclusion criteria in this study were active schizophrenic patients aged 18-45 years old who did not have physical comorbidities and whose family or guardians gave their consent for participation in the study. Informed consent was carried out directly to the patient's guardian who was present at Dr. Amino Gondohutomo Regional Psychiatric Hospital. Schizophrenia diagnosis was determined with ICD-10 disease code. F20 (Schizophrenia), F20.0 (Paranoid Schizophrenia), F20.1 (Hebephrenic Schizophrenia), F20.2 (Catatonic Schizophrenia), and F20.3 (Undifferentiated Schizophrenia) were among them. Exclusion criteria in this study were the following: uncooperative patients and those who had other neurological and vascular disorders that affect cognitive function (e.g., history of stroke).

Study process and data gathering

The study began by surveying the Emergency Room (ER) at Dr. Amino Gondohutomo Regional Psychiatric Hospital. This was carried out from June 27 to July 2, 2022. The psychiatric resident on duty at Dr. Amino Gondohutomo Regional Psychiatric Hospital confirmed whether schizophrenic patients who presented to the ER met the inclusion and exclusion criteria. If they met the criteria, the patient's guardian would then be interviewed by the researcher whether they allow the patient to participate and whether the patient's medical record data can be accessed. This was conducted by filling out an informed consent form. Upon consent, then the patient as the subject of the study was examined for cognitive function using the MoCA-Ina questionnaire to determine the level of cognitive function of the patient. Then, the patient's blood serum was taken by a local laboratory assistant. The blood serum was then sent to the laboratory to be checked for Vitamin D levels.

Data processing and statistical analysis

The SPSS 26.0 program was then used to statistically analyze the collected data. Univariate analysis was conducted to process the data on the characteristics of the patients (age, gender, education level, and occupation), which will be displayed in the form of a descriptive table. The hypothesis of this study was tested using correlation test using the SPSS 26.0 program. The data normality test was performed using Saphiro–Wilk test (n<50), then continued with the Pearson correlation test. The correlation between serum Vitamin D levels of schizophrenic patients and their cognitive function is significant if the correlation test result is $p<0.05$ with a 95% confidence interval. In addition, the data will also be assessed for correlation strength between the two variables and the nature of the correlation.

Results

The results of the descriptive analysis of research subject characteristic are listed in Table 1.

Table 1 shows the characteristics of 18 people who participated in this study. The average age of the research subjects was 33 years, with a 19-year-old as the youngest participant and a 43-year- old as the oldest. Most of the research subjects were men, precisely 11 people (61.1%). In addition, 11 people (61.1%) did not have a job or were in a state of not working when the research was conducted, 3 people are working as private employees (16.7%), 2 people are working as an entrepreneur (11.1%), and 2 people are doing other jobs, namely, teachers and factory workers (11.1%). The educational background of the research subjects also differed, with 9 of them having completed high school level (50%), 7 having less than 12 years of education (38.9%), and only 2 having more than 12 years of education (11%).

Table 1. Research subject characteristic.

Variable	Frequency (n)	(%)
Age at index date (years)		
18–25	3	16.7
26–35	9	50
36–45	6	33.3
Sex		
Male	11	61.1
Female	7	38.9
Occupation		
Unemployed	11	61.1
Private employee	3	16.7
Entrepreneur	2	11.1
Others	2	11.1
Educational background		
No educational background	1	5.6
Elementary school	2	11.1
Junior high school	4	22.2
High school	9	50
Bachelor or higher	2	11

Table 2 shows a descriptive analysis of MoCA-Ina scores and serum Vitamin D levels. The MoCA-Ina scores of all research subjects were in the category of "cognitive impairment" with an average score of 15.72. The subjects' serum Vitamin D levels also mostly showed Vitamin D deficiency (13 people) with the rest having Vitamin D insufficiency status. The average Vitamin D level of the subjects in this study was 16.3 ng/dL.

Table 2. Observed Vitamin D level and MoCA-Ina score.

Variable	F	%	Mean	Median
MoCA-Ina score			15.72	16.5
Normal	0	0		
Cognitive impairment	18	100		
Vitamin D serum level			16.3	17.65

Insufficiency	5	27.8
Deficiency	13	72.2

Table 3 and Figure 1 show the results of the MoCA-Ina questionnaire conducted to the research subject. Based on the tables and figures, data were obtained based on the score in each of the cognitive domains tested. In the visuospatial/executive domain, the average score obtained by the research subjects was 2.5 out of 5 maximum scores. The average naming score is 2.63 out of 3.

Table 3. MoCA-Ina score of each cognitive domain.

Cognitive domain	Mean ± SD	Score (min-max)
Visuospatial/executive	2.5 ± 1.25	0–5
Naming ability	2.67 ± 0.77	0–3
Attention	2.94 ± 1.98	0–6
Language	1.39 ± 1.14	0–3
Abstraction	0.83 ± 0.79	0–2
Memory	1.33 ± 1.71	0–5
Orientation	3.17 ± 2.09	0–6

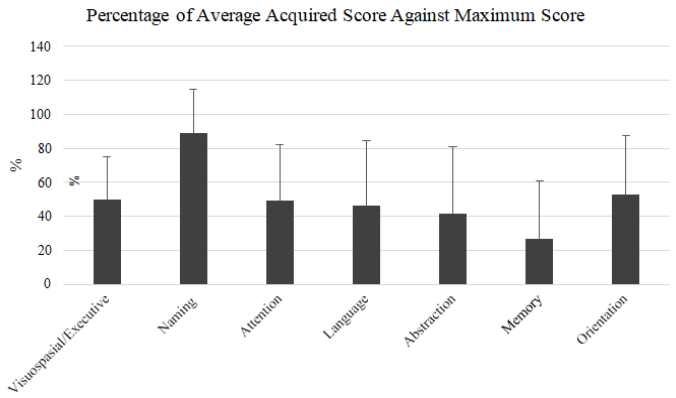

Figure 1. Percentage of subject ability to do MoCA-Ina questionnaire.

The average attention domain score is 2.94 out of 6. The average language domain score is 1.39 out of 3. The average abstraction domain score is 0.83 out of 2. The memory domain is 1.33 out of 5. In the orientation domain, the average score of the research subjects is 3.17 out of 6.

The results of the Pearson correlation test are p=0.039 and r=0.490. The result of p=0.039 showed that the correlation between serum Vitamin D levels and cognitive function impairment is significant. According to this correlation, changes in serum Vitamin D levels of schizophrenic patients will be followed by changes in the MoCA-Ina score, which describes the cognitive function of these patients. The strength of the relationship or correlation of these two variables is r=0.490. This indicates that the strength of the relationship is moderate with the nature of the relationship being positive. The positive nature indicates that if there is an increase in serum Vitamin D levels, there will be an increase in the MoCA-Ina score. Conversely, if there is a decrease in serum Vitamin D levels, there will also be a decrease in the MoCA-Ina score.

Discussion

In this study, cognitive function assessed from the MoCA-Ina score on 18 research subjects showed an average of 15.72, and none of this study subjects had a MoCA-Ina score of more than 25. This indicates that all study subjects have cognitive impairment. All cognitive domains that can be assessed from the MoCA-Ina research instrument also appear to experience various declines in various research subjects. These results confirm the results obtained in previous studies, which showed a decline in function, especially in seven cognitive domains, namely, verbal memory and learning, visual memory and learning, working memory, social cognition, attention and alertness, processing speed, and reasoning and problem solving [15].

Vitamin D levels obtained from serum samples of research subjects had an average of 16.3 ng/dL. This shows that the research subjects, on average, have Vitamin D deficiency in their bodies. The results of this study are in accordance with previous research, which states that schizophrenic patients have low levels of Vitamin D in their bodies [12,13].

This study also supports the theory of Vitamin D as a pathophysiology of schizophrenia. This theory states that low levels of Vitamin D result in a lack of anti-inflammatory response, which plays an important role in suppressing the production of kynurenic acid. Kynurenic acid is an NMDA receptor antagonist that plays an important role in brain neurotransmission [8].

In this study, it has been found that there is a correlation between serum Vitamin D levels and impaired cognitive function in schizophrenic patients, as shown in Table 4. The correlation between low serum Vitamin D levels and the severity of cognitive impairment in schizophrenic patient is positive with a moderate strength of correlation. This statement shows that there is conformity between this research and previous research [17].

Table 4. Pearson correlation analysis.

Variable	Correlation coefficient value (r)	MoCA-Ina score
Vitamin D (ng/mL)		0.49
Significance value (p)		0.039
Total sample (n)		18

From previous research, the decrease in Vitamin D levels does not have a significant relationship or correlation with positive and negative symptoms of schizophrenia patients as measured using the PANSS (Positive and Negative Syndrome Scale) score. However, these studies also revealed that negative symptoms and cognitive impairment had a significant relationship with decreasing Vitamin D levels in schizophrenic patients. In the current study, it is also proven by using the MoCA-Ina, an instrument that specifically assesses various cognitive domains of patients, that there is a significant correlation between decreased levels of Vitamin D and the severity of cognitive disorders experienced by schizophrenic patients [18].

The difference in the effect of Vitamin D on positive symptoms with the effect of Vitamin D on negative symptoms and cognitive function can be presumed due to differences in the neurotransmission pathways through which they pass. From the research that has been conducted by Brisch, et al. it was found that the appearance of positive symptoms in schizophrenic patients was due to the presence of excessive dopamine [19]. Excessive release may affect the activity of dopamine D2 receptors, which play an important role in the pathophysiology of positive symptoms in schizophrenic patients. The cause of the excessive occurrence of dopamine is due to disturbances in the nucleus accumbens and hippocampus (mesocorticolimbic pathway). This statement is also supported by several studies that carry out stimulation and therapy in these two areas. These stimulation and therapy resulted in the improvement of positive symptoms in schizophrenic patients [18,19].

Differences occur in the effect of Vitamin D on negative symptoms and cognitive function of schizophrenic patients. Vitamin D has been shown to decrease the production of inflammatory cytokines in the body. Low levels of inflammatory cytokines can cause inhibition of tryptophan metabolism so that metabolites, such as kynurenic acid, an NMDA receptor antagonist, decrease in number. Antagonism of the NMDA receptor is a theory of the pathophysiology of schizophrenia. This pathway starts from the frontal

cortex area, where the antagonistic glutamate receptors then send minimal signals to the GABA (Gamma-Aminobutyric Acid) interneurons. GABA interneurons with this minimal stimulus then release small amounts of GABA at other glutamate receptors in the thalamus. Because GABA is an inhibitory neurotransmitter, this glutamate neuron will then be hyperactivated. This will cause overstimulation of other GABA interneurons. This then causes the release of large amounts of GABA, which then inhibits mesocortical pathways, causing negative symptoms [20]. This proves that NMDA receptors play a role in the positive symptoms of schizophrenia and, more significantly, play a major role in the negative symptoms and cognitive function of schizophrenic patients. NMDA receptors that work properly can reduce the severity of negative and cognitive symptoms in schizophrenic patients [21,22].

With the significance of NMDA receptors in cognitive function of schizophrenic patients known, it can be inferred that Vitamin D, which effect inflammation and NMDA pathway, supplementation might have beneficial effect on improving cognitive symptoms of schizophrenic patients. Further studies need to be conducted on Vitamin D supplementation on schizophrenic patients and its effect to cognitive function. However, supplementation is not the only way as behavioral change, for example bathing in the sun, can also increase Vitamin D synthesis thus increasing Vitamin D levels in the blood.

The limitation of this study is that it does not limit the length of time the patient has suffered from schizophrenia. In addition, no restrictions were placed on the category of schizophrenic episodes taken. This is due to the limited time and research resources available. Another weakness in this study is that there are no restrictions on the drugs, which have been consumed in the research subjects, such as typical and atypical antipsychotics. This weakness is also difficult to anticipate because many patients who have come to the ER as subjects have taken antipsychotic drugs.

Conclusion

There is a positive correlation between serum Vitamin D levels and cognitive function in schizophrenic patients with moderate strength. The correlation that was found in this study indicates that Vitamin D plays an important role in schizophrenia and its therapy. Vitamin D can reduce the severity of negative symptoms hence improving cognitive function. This will benefit not only the hospital that provide the treatment but also the patient where better symptoms result in better quality of life and discharge time. Further study needs to be conducted to confirm this finding. Further experimental study can also be done where subjects with schizophrenia will be given additional dose of Vitamin D in to their therapy.

Future studies may limit the length of time patients suffer from schizophrenia who can be taken as research subjects. It can also be restricted to only first-episode schizophrenic patients. In addition, it is necessary to control the consumption of drugs in research subjects. This can be conducted to avoid the cognitive function of schizophrenic patients, which worsens with the length of time the patient suffers from schizophrenia and the drugs used.

Data Availability Statement

The data sets used during the current study are available from the corresponding author upon reasonable request.

Author Contribution

AD and WS conceived and designed the research protocol. AD and SW did the data collection. WS, NW, and AF revised the manuscript. All authors contributed to the article and approved the submitted version.

Ethics Approval and Consent to Participate

This study was conducted after obtaining ethical clearance from the Health Research Ethics Commission (KEPK) Faculty of Medicine, Diponegoro University number 116/EC/KEPK/FK- UNDIP/V/2022, which is valid until May 12, 2023. In addition, this research has also received ethical clearance from KEPK RSJD Dr. Amino Gondohutomo number 420/09482. The identity of the research subjects and the data obtained are kept confidential and are only used for research purposes.

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Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest. We wish to thank the all staff of inpatient and emergency department of Amino Gondohutomo Regional Psychiatric Hospital for their collaboration on this study.

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