The role of vitamin deficiency

by Azimatul Karimah

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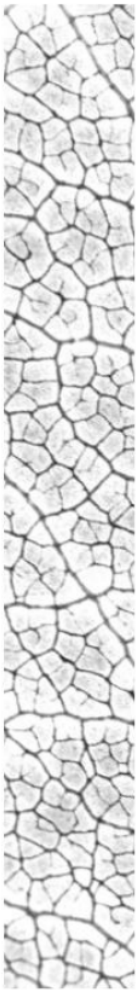

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The role of vitamin d deficiency towards cognitive deficit of schizophrenia

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Abstract

Background: Vitamin D receptor (VDR) discovery in the brain tissue demonstrates clearly that vitamin D has a significant role in the development of the brain. This study aimed to analyze the correlation between serum vitamin D levels and cognitive deficits in schizophrenic patients.
Methods: This was an observational analytic study with cross-sectional design. Serum vitamin D levels were measured using VIDAS® 25 OH Vitamin D Total (VITD). Cognitive deficits were measured using Indonesian version of the Schizophrenia Cognition Rating Scale (ScoRSvI).
Results: This study recruited 54 patients from outpatient and inpatient unit of psychiatric. Most of subjects were male as many as 25 (65.8%). Mean age of subjects was 34.84 years. Mean duration of illness was 10.58±7.4 years. There were 17 (45%) subjects experienced serum vitamin D deficiency, and 22 (58%) study subjects had cognitive deficits on the global impression of ScoRSvI assessment by rater. There was a significant negative correlation ($p < 0.001$) between serum vitamin D levels and SCoRSvI values from the impression of global observations, ScoRSvI patients, and ScoRSvI informants.
Conclusion: The lower serum vitamin D levels, the higher score of cognitive deficits from SCoRSvI. The higher SCoRSvI score shows the more severe cognitive deficit for patients with schizophrenia.

Keywords: schizophrenia, serum vitamin D levels, cognitive deficits

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INTRODUCTION

The most prevalent disorder in a group of psychotic disorders is schizophrenia (Catherine et al. 2018). Schizophrenia is a heterogeneous condition between the genetic and environmental factors that combines and leads to the severity of the disease (Hidayati et al. 2014, Samoes et al. 2017). Since it has been discovered, microorganisms like Helicobacter pylori have been involved in a variety of extra-digestive diseases that may have a potential role in psychiatric disorder pathogenesis which triggers dopaminergic dysfunction (Miftahussurur et al. 2017). In addition, Indonesian people have brown skin. Indonesia, geographically located at the line 06°08' north latitude - 11° 5' south latitude with a tropical climate allows sunlight to be radiated intensively throughout the territory of Indonesia (Ministry of Environment of the Republic of Indonesia 2011). Vitamin D deficiency risk factors are dark skin color and insufficient exposure to the sun (McGrath et al. 2010, Mutsatsa et al. 2013). Vitamin D is analyzed through 25-OH levels of vitamin D (calcidiol), a form that circulates in the circulation making it possible to do assessments of Vitamin D levels in the body (Amaral et al. 2014).

Schizophrenia can be treated by minocycline which may be a potential therapeutic drug for to improve recognition memory (Liaury et al. 2014). Whereas, another report revealed that occupational therapy was effective when combined with antipsychotic therapy and the group psychotherapy to improve cognitive function and the quality of life of the schizophrenia patients, especially in long term therapy (Coymak, 2019, Idrus et al. 2019). Cognitive deficits are a major source of functional and social disorder in schizophrenia and have a more positive and negative effect on everyday life (Homayoun et al. 2011), which appears to be a problem in daily activities and is related to internal goals and motivation (Falkenberg et al. 2014). Considering various

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Table 1. Characteristics of subjects

Characteristics	Results
Sex	
Male	25 (65.8 %)
Female	13 (34.2 %)
Education	
Elementary school	1 (2.6%)
Junior high school	6 (15.8%)
Senior high school	26 (68.4%)
Bachelor	2 (5.3%)
Category of schizophrenia	
Paranoid	24 (63.2 %)
Hebephrenic	7 (18.4 %)
Catatonic	1 (2.6 %)
Undifferentiated	5 (13.6 %)
Residual	1 (2.6 %)
Age of symptom onset	
≤ 18 years	11 (28.9 %)
> 18 years	27 (71.1 %)
Duration of illness	10.58±7.431

Table 2. Serum Vitamin D levels and SCoRSvI of subjects

Variables	Results
Serum Vitamin D levels (ng/ml)	23.15±8.197
Deficiency (<20 ng/ml)	17 (45%)
Insufficiency (20-29 ng/ml)	12 (31%)
Sufficient (30-100 ng/ml)	9 (24%)
ScoRSvI interviewer	2.32±1.454
Cognitive deficit	22 (52%)
No cognitive deficit	16 (48%)
ScoRSvI patients	24.16±5.607
ScoRSvI informants	24. 21±5.7

Table 3. Correlation between Serum Vitamin D levels and SCoRSvI

Variables	r	p value
Serum Vitamin D levels with ScoRSvI interviewer	-0.736	<0.001
Serum Vitamin D levels with ScoRSvI patients	-0.719	<0.001
Serum Vitamin D levels with ScoRSvI informants	-0.696	<0.001

previous studies show the controversy of the relationship of vitamin D deficiency (VDD) with cognitive deficits, as well as considering the importance of vitamin D for mental health (Sotodeh-Asl et al. 2014), we hypothesized that serum VDD influence cognitive deficits on schizophrenic patients undergoing treatment at Dr. Soetomo General Academic Hospital, Surabaya. This study aimed to analyze the correlation between serum vitamin D levels and cognitive deficits in schizophrenic patients (Rajuddin Rajuddin*, Rudy Harahap 2019).

METHODS

This was an observational analytic study of schizophrenia patients who received treatment at Dr. Soetomo General Academic Hospital Surabaya, Indonesia, with cross sectional design. The inclusion criteria of the study were: a) patient who recieved diagnosis schizophrenia according to ICD X criteria, b) aged 18-45 years, c) patients did not consume medication which affecting to serum vitamin D level (e.g bronchodilators, hormonal drugs, anti-hypertension, antibiotics, antiepileptics, antineoplastic , anti-inflammatory, antiretroviral, endocrine drugs, teophylline, isoniazid, rifampizin, cimetidine, cholestramin) in the last 7 days, d) both patients and caregivers gave consent to participate in this study, and e) speaking Indonesian fluently. We excluded patients who had mental retardation (screened by clinical psychologist), known having physical comorbidity affecting serum vitamin D level (screened using liver function and renal function test). Serum vitamin D levels were measured using VIDAS® 25 OH Vitamin D Total (VITD). Cognitive deficits were measured using Indonesian version of the Schizophrenia Cognition Rating Scale (SCoRSvI). Statistic was analyzed by SPSS using the Spearman correlation test.

RESULTS

This study involved 38 subjects, most of them were 25 males, with a mean age of 34.84 years old, had symptom onset when they were over 18 years old, with the lowest age range of 13 years old and the higest age of 36 years old. In this study, mean of duration of illness was 10.58±7.4 years, with a range of duration of illness between 1-28 years (**Table 1**). The results of the analysis in this study are shown in **Table 2**. The mean of serum vitamin D levels was 23.15±8.197 ng/mL, with range of 8.1-37.6 ng/mL. The serum vitamin D level in 17 (45%) subjects was deficiency (<20 ng/mL), 12 (31%) were insufficiency (20-29 ng/mL), and 9 (24%) were suficient (30-100 ng/mL). There was a mean SCoRSvI score of global observational impressions from the interviewer ratings of 2.32±1.454, with the lowest score range of 1 and the highest score of 6. There was a cognitive deficit of 22 (52%) global observational impressions.

Table 3 presents correlation results. There was significant negative correlation between serum vitamin D levels and SCoRSvI interviewer of global observations impression ($p < 0.001$, $r = -0.736$), ScoRSvI patients ($p < 0.001$, $r = -0.719$) and ScoRSvI informants ($p<0.001$, $r = -0.696$). The lower of serum vitamin D levels, the higher score of cognitive deficits obtained in ScoRSvI (**Fig. 1**). There was significant difference on SCoRSvI score of subjects who had more outdoor activities compare to more indoor activities, for patient rating ($p = 0.027$, $r = 0.028$) and informant rating ($p = 0.044$, $r = 0.45$). Subjects with a duration of sun exposure ≤ 60 minutes had a score of SCoRSvI higher than the subjects with a duration of sun exposure > 60 minutes. We found significant differences of SCoRSvI score between subjects who had less and more sun exposure rated by interviewer ($p = 0.011$, $r = 0.016$), from patient rating ($p = 0.003$, $r = 0.003$), and from informant rating ($p = 0.005$, $r = 0.004$). Significantly, subjects with less sun exposure (≤ 60 minutes/day) gained higher SCoRSvI score compared to subjects with more sun

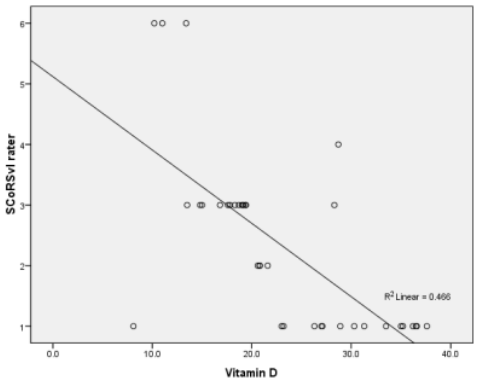

Fig. 1. Plot chart shows the correlatio between serum vitamin D levels and SCoRSvl rater

exposure (> 60 minutes/day). It means that with more sun exposure, subjects had less cognitive deficit. The majority of subjects were exposed to the duration of sunlight before 12.00 a.m. ≤ 60 minutes. The majority had the type of activity indoors and obtained serum vitamin D deficiency. Researchers suspected that the research subjects were exposed to less sunlight.

DISCUSSION

Our analysis has demonstrated serum vitamin D levels in schizophrenic patients correlated with cognitive deficits. Vitamin D enhances tyrosine hydroxylase expression in the adrenal medullary cells, implying that vitamin D can modulate the dopaminergic procedure (Eserian 2013). The dopamine theory suggests that dopamine dysfunction is central to the pathogenesis of schizophrenia (Kesby et al. 2013). In Schizophrenia patients, the attention, concentration, verbal and visual memory tests and output tests show substantially cognitive shortfalls, and nearly all test results are worse as compared to normal controls (Krishnadas et al. 2007). The extent of this disorder, schizophrenia is concluded as a complex neurodevelopmental disorder with a global profile of cognitive impairment as a major part (Bowie et al. 2006, Utami et al. 2018). Some cognitive approaches in combination with other therapeutic methods could improve the physical function of chronic pain patients, such as schizophrenia (Afrina et al. 2019).

The geographical position of a Vitamin D deficiency in schizophrenia also affects the sun exposure of people who live in the region (Akbar et al. 2018). This study was conducted in Surabaya, Indonesia which is located in the Indonesian territory with the location of low latitude and intensive sun exposure in all regions of Indonesia. VD, which is also called sunshine vitamin, requires exposure time every day 1-2 hours to maintain serum vitamin D levels, which are carried out in urban Indian men aged 40-60 years. Excessive exposure to sunlight >2 hours every day cannot linearly increase serum vitamin D levels (Patwardhan et al. 2018). Conversely, another study found that UVB reception from sun exposure for 25 minutes, 3 times a week, for 6 weeks can increase serum vitamin D levels, in elderly women ≥60 years old in Jakarta and Bekasi. The optimal time for sun exposure is 1 hour before and after noon, but the heat of the sun when midday, 11.00 - 13.00, causes discomfort and avoidance of sun exposure, thus the recommended time for sun exposure is 9 am (Setiati et al. 2007).

Vitamin D has several roles in the brain. In dopamine transmission, low levels of vitamin D cause Catechol-O-methyl-transferase (COMT) to down-regulation in the forebrain, which causes a decrease in HVA concentration, which is a marker of dopamine activity. Reduction in homovallinic acid (HVA) levels in prefrontal cortex (PFC) is associated with poor working memory in schizophrenia (Amaral et al. 2014). Vitamin D is a strong inducer of the glial cell line-derived neurotrophic factor (GDNF), capable of enhancing the survival of dopaminergic neurons. GDNF participates in the development of dopaminergic pathways and immediately regulates dopaminergic cell apoptosis in substantia nigra after birth. Vitamin D affects the dopamine pathways in the brain neuroprotectively, that is when 6-hydroxydopamine (6-OHDA) which is a dopaminergic selective poison is administered to animals pre-treated with 1,25-(OH)2D3 for 1 week, getting dopaminergic function is maintained. Evidence is obtained that DVD deficiency in neonatal rats has reduced GDNF expression in the brain (Eserian 2013).

Mesocortical dopamine pathway is the pathway from the cell body in the area of the ventral tegmentum to the prefrontal cortical area. Branches from this pathway to the dorsolateral prefrontal cortex (DLPFC) regulate cognitive and executive functions. Deficit dopamine activity starting from mesocortex to DLPFC causes cognitive symptoms in schizophrenia (Stahl et al. 2013). Interaction of vitamin D with calcium channels on the development of schizophrenia is related to parvalbumin calcium-binding proteins (CBP) expression. The low prenatal vitamin D supply significantly changes CBP expression. The decrease in parvalbumin-positive neurons has increased the incidence of schizophrenia, through down regulation of Lhx6 which is an essential transcription factor for migration and maturation of parvalbumin-positive neurons. Decreased GABAergic neurotransmitters between parvalbumin-positive interneurons and pyramid cells are believed to support impaired working memory in schizophrenia (Amaral et al. 2014).

In previous research, lower serum vitamin D levels were related to serious cognitive deficits in young adult patients, assessed using the summary cognition value and lower verbal fluency scores. This can be caused by

schizophrenia patients suffering from negative symptoms and/or extreme cognitive deficits leading to lower serum vitamin D levels. Symptoms that appear include: social isolation, no motivation, which is related to the overall lower level of function which has the potential to cause poorer nutrition which causes less time spent outdoors which ultimately contributes to lower serum vitamin D levels (Graham et al. 2015).

Limitations of this study include only analyzing serum vitamin D levels and SCoRSvI scores in schizophrenic patients without taking into account other therapies given during treatment. This raises the possibility of different treatments for each research subject to the different psychopharmaceuticals given, so that further research is needed with a larger population with longer observations than this study to compare the relationship between serum vitamin D levels and cognitive deficits in schizophrenic patients by controlling other confounding factors, such as controlling therapy. In this study, the measurement of serum vitamin D levels was carried out with a tool that measured serum total vitamin D (vitamin D2 and D3) levels, so it was necessary to research with serum vitamin D levels that were more specific to differentiate vitamin D2 and D3 levels. SCoRSvI cognitive measurement instrument evaluates attention, memory, reasoning and problem solving, working memory, language production and motor skills, without grouping each question into these cognitive domains. Thus, other cognitive measurement instruments are needed to be able to evaluate more specifically of what aspects of the cognitive domain are disturbed.

CONCLUSION

There is evidence of a correlation that the lower serum vitamin D levels the more severe the cognitive deficits of schizophrenic patients, so if possible, schizophrenic patients need to be exposed to sunlight routinely, and of course still given antipsychotics as the main therapy. Thus, improvement in cognitive symptoms is obtained and patients get more treatment well.

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