RESEARCH ARTICLE

MCBS

Vitamin D Status and Cognitive Performance of Post Stroke Patients

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Background: The prevalence of post-stroke cognitive impairment (PSCI) ranges from 20-80%. Some studies found that vitamin D deficiency was common in stroke patients, yet the relationship with cognitive performance remains unclear. The study aimed to investigate the relationship between levels of vitamin D and cognitive performance in post-stroke patients.
Materials and Methods: This was a cross-sectional study with 20 post-ischemic stroke patients. Vitamin D levels were measured using enzyme-linked fluorescent assay (ELFA). The cognitive performance was assessed by computerized mini-mental state examination (MMSE) and clock drawing test (CDT). The relationship between vitamin D levels and cognitive tests were performed using paired T-test.
Results: Vitamin D insufficiency (<30 ng/mL) was experienced by all of the study subjects (100%), with the mean±SD of vitamin D level was 13.75±4.06 ng/mL. More than 70% subjects had cognitive impairment. Based on MMSE, patients with cognitive impairment had lower vitamin D levels, compared with those patients with normal cognition (13±4.38 *vs.* 16±2.44 ng/mL, *p*<0.001). In CDT examination, patients with cognitive impairment had slightly higher vitamin D levels, compared with those patients with normal cognition (13.93±4.25 *vs.* 13.33±3.93 ng/mL, *p*<0.001).
Conclusion: The insufficiency of vitamin D on post-ischemic stroke patients appears to generate a bigger chance of PSCI occurrence. Physicians should be aware of vitamin D status of post-stroke patients, especially in the older population.

Keywords*: vitamin D levels, post-stroke cognitive impairment, risk factors*

Introduction

Vitamin D is a fat-soluble vitamin that mainly responsible for calcium and phosphorus metabolism and bone mineralization.(1) Vitamin D deficiency is a very common problem and arises from multiple causes, including inadequate dietary intake and inadequate exposure to sunlight or certain medical condition. The epidemiological data on the previous study has report one billion cases of worldwide vitamin D deficiency, with the highest prevalence in the elderly, obese patients, nursing home residence, and hospitalized patients. The previous study also reports of

vitamin D insufficiency prevalence that reaches as much as 50% of the population.(2)

Stroke is the second most common cause of death globally and leads to 9% of all deaths. Hypertension, hyperlipidemia, smoking, diabetes mellitus, obesity, and atrial fibrillation are among the modifiable risk factors for ischemic stroke. In 2018, stroke was the leading cause of in-hospital mortality based on the Indonesian Basic Health Survey.(3) Recent studies showed that vitamin D deficiency was found in stroke patients. Vitamin D deficiency was associated with hypertension, hyperlipidemia, and diabetes (all the vascular risk factors for stroke).(3-5).

Previous studies either in animals and humans suggest that impaired brain physiological function might happen because of vitamin D deficiency. There is also proof that vitamin D had a protective ability against biological processes associated with Alzheimer's disease and cognition. (6,7) There are limited data from the Indonesian series on the correlation between vitamin D with brain function and cognition, especially with the post-stroke cognitive function. Thus, this study aims to investigate the correlation between Vitamin D levels and cognitive performances of post-ischemic stroke patients in Bethesda hospital Yogyakarta Indonesia.

Materials and methods

This retrospective study was approved by the Bethesda Hospital Ethics Committee with ethical approval letter No. KEP/RS Bethesda/376. Oral informed consent was obtained from all study participants followed by each of them signing a letter of approval to be the respondent in this study.

Study Population
We used consecutive sampling, where subjects were recruited within a period of 1 month. The inclusion criteria were patients older than 18-year-old and diagnosed with ischemic stroke. The diagnosis of ischemic stroke was made by a neurologist based on neurological and radiological examination.

Data Collection
Patients' data were obtained from the electronic medical record and information system of Head Computed Tomography (CT) scan of hospital stroke registry. The data of cognitive performance was measured by standard computerized mini-mental status examination (MMSE)

and clock drawing test (CDT) test in the memory clinic at Bethesda Hospital, Yogyakarta. MMSE score of <24 out of 30 and/or CDT score ≤2 out of 4 were indicated as cognitive and memory impairment. MMSE and CDT were proved as valid tools to evaluate subjects with mild cognitive impairment (MCI) while also capable of differentiated patients with various types of dementia. The affordable and easy to used nature of both test are another advantage that makes standard computerized MMSE and CDT test were considered to be used in this study.(8) CT scan examination on study respondents was carried out on the same day the patient was admitted to the hospital. MMSE and CDT examinations in patients were carried out within the same week to <14 days from the day the patient was hospitalized The vitamin D level was measured with a standardized laboratory method using enzyme-linked fluorescent assay (ELFA). The measurement was carried out with serum or plasma that will be examined on VIDAS® 25OH Vitamin D (bioMérieux, Marcy l'Etoile, France). In this study, we measured the 25-hydroxyvitamin D [25(OH)D] which was the inactive form of vitamin D and the major form found in the blood to assess vitamin D status in participants. Vitamin D deficiency had been defined as levels of 25(OH)D less than 20 ng/mL, while levels below 30 ng/mL indicate vitamin D insufficiency.(9)

Data Analysis
Percentages and count were used for represented the categorical variable while mean and standard deviation (SD) were used for normally distributed data on baseline data. Due to the small number of respondents, the normality test was done using the Shapiro-Wilk test. Correlations between the vitamin D level and cognitive performance were measured by paired T-test. Statistical analysis was performed using the SPSS 26.0 software (IBM SPSS Statistics, New York, USA). The level of significance was set at $p<0.05$.

Results

A total of 20 subjects with a history of ischemic stroke were included in the study. Their clinical characteristics were shown in Table 1. Their mean±SD age was 67.7±9.4 years, and 11 were male patients (55%). All of these patients had at least 1 of the following underlying disorders: hypertension (20%), diabetes (30.0%), and dyslipidemia (75%). Five patients (20%) also had a history of cigarette smoking in the past. Based on the head CT scan imaging, most of

Table 1. Clinical characteristics of post-stroke patients.

Characteristics	Value (n=20)
Age (year), mean±SD	67.7±9.4
Sex, n (%)	
Male	11 (55)
Female	9 (45)
Comorbidities, n (%)	
Hypertension	4 (20)
Diabetes	6 (30)
Dyslipidemia	15 (75)
History of Smoking, n (%)	
Yes	5 (25)
No	15 (75)
Infarct Location, n (%)	
Not visible	7 (35)
Frontal lobe	0 (0)
Parietal lobe	4 (20)
Temporal lobe	1 (5)
Multiple locations	8 (40)
Medication, n (%)	
Anti-platelet	20 (100)
Statin	14 (70)
Citicoline	4 (20)
Vitamin D (ng/mL), mean±SD	13.75±4.06
Vitamin D Levels, n (%)	
Sufficient ($\geq$ 30 ng/mL)	0 (0)
Insufficiency (<30 ng/mL)	20 (100)
MMSE score, mean±SD	19.15±4.26
MMSE Score, n (%)	
$\geq$ 24 (normal)	5 (25)
< 24 (cognitive impairment)	15 (75)
CDT Score, mean±SD	1.35±1.42
CDT Score, n (%)	
>2 (normal)	6 (30)
$\leq$2 (cognitive impairment)	14 (70)

the patients had multiple locations of infarct (40%). In 7 patients, the location of the stroke was not visible through the scan.

     All the patients received antiplatelet such as aspirin or clopidogrel for their post-stroke treatment. Fourteen patients (70%) received statins, and 4 patients (20%) received citicoline. All of the patients in this study had insufficiency (<30 ng/mL) levels of vitamin D, with the mean level was 13.75±4.06 ng/mL. Their cognitive performance was measured using 2 scales including MMSE and CDT. From the MMSE examination, most of the patients had cognitive impairment (75%). Similarly, the CDT examination showed cognitive impairment (70%) was common in our patients.

     Table 2 showed the comparison of vitamin D levels in cognitive impairment and normal patients based on MMSE total score. Patients with cognitive impairment had lower vitamin D levels, compared with those patients with normal cognition (13±4.38 ng/mL *vs.* 16±2.44 ng/mL; p<0.001). The comparison of vitamin D levels in cognitive impairment and normal patients based on CDT total score was also shown in Table 2. Patients with cognitive impairment had slightly increased vitamin D levels, compared with those patients with normal cognition (13.93±4.25 ng/mL *vs.* 13.33±3.93 ng/mL; *p*<0.001).

Discussion

Ischemic stroke is a major cause of death and long-term disability globally. The result showed that all of the study subjects have low vitamin D levels (< 30 ng/mL), thus make them diagnosed by vitamin D insufficiency. Some studies showed that there is a relation between vitamin D deficiency with the risk and prognosis of ischemic stroke patients. (10,11) The mechanism was explained by recent findings on vitamin D roles in influencing atherosclerosis forming by regulating inflammatory activity within vascular walls and regulating renin production, thus attenuating hypertension. (12,13)

     Cognitive measurements using MMSE and CDT on all subjects in this study showed most of the post-ischemic stroke patients with vitamin D insufficiency had cognitive impairment. This might imply that post-ischemic stroke patients with vitamin D insufficiency tend to undergo PSCI. This result was consistent with a previous study that showed a 2,124-fold increase in the risk of PSCI on patients with vitamin D deficiency.(14)

     There has been a detailed explanation of how PSCI might occur on post-stroke patients, but there is no detailed explanation yet of how vitamin D can affect cognitive function. A recent trial study in Japan, showed low vitamin D levels are related to poor prognosis after stroke. Still, whether vitamin D supplementation of post-stroke patients can improve these outcomes remains unclear.(15)

     Another study found that vitamin D showed an ability to initiate neurogenesis and regulated the synthesis of several neotropics factors that influence neuronal growth,

Table 2. Comparison of vitamin D levels and cognitive performance on MMSE and CDT.

Examination Type	Vitamin D Levels (ng/mL) mean±SD		95% CI	*p*-value
	Cognitive Impairment Group	Normal Group		
MMSE Score	13.00±4.38	16.00±2.44	10.02-13.98	<0.001
CDT Score	13.93±4.25	13.33±3.93	10.33-14.47	<0.001

differentiation, and maturation.(16) That was considered as something that might be related to the development of PSCI in a previous study.(14)

There is a difference in the number of respondents who experienced PSCI which the MMSE examination finds more patients with PSCI (n=16) than the CDT examination (n=15). This difference result could happen because of the lack of sensitivity of the CDT compared with MMSE, thus make CDT possibly detected fewer patients with PSCI then MMSE.(17)

There is also been found a slightly higher vitamin D concentration in PSCI patients compared with the normal patients in the CDT result (13.93 ng/mL *vs.* 13.33 ng/mL). This result was contradictory to our hypothesis on how a lower vitamin D concentration brought a greater risk of PSCI. We believed that it is important to take into account how the vitamin D concentration on both groups was already considered as vitamin D insufficient and the vitamin D concentration was just being slightly different (0.6 ng/mL).

This study managed to present information about Vitamin D levels and cognitive performances of post-ischemic stroke patients. However, it has several limitations, such as an absence of post-ischemic stroke patients with normal vitamin D levels included as a comparison and the limited number of stroke subjects due to the short timeframe of this study. This study also did not take into account the other risk factors of PSCI that have already been diagnosed in patients. We encourage further study to do a comparison test between a PSCI diagnosed group and a normal cognitive group. We also suggest doing the test of homogeneity on each group to reach a more pragmatic result.

Conclusion

The insufficiency of vitamin D in post-ischemic stroke patients appeared to generate a bigger chance of PSCI occurrence, based on the high rate of PSCI cases in the result. The CDT lack of sensitivity might become a reason for the difference in the MMSE and CDT result in this study. There is no detailed information on the mechanism of vitamin D on cognitive function, but there are new findings on vitamin D roles in brain health and function that might relate to PSCI cases in post-stroke patients.

Acknowledgments

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