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Vitamin D Deficiency in Some Neurological Disorders in Sohag Teaching Hospital, Upper Egypt

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ABSTRACT

Vitamin D Deficiency (VDD) has become a worldwide public health problem. It is well known that adequate vitamin D is important for optimal function of many organs and tissues throughout the body. We constructed a research plan in the form of a case control study aiming to detect of the frequency of VDD in some neurological disorders in comparison to control group. We choose cerebrovascular strokes and neuromuscular disorders from patients visiting the outpatient Neuropsychiatry clinic of Sohag Teaching Hospital in Upper Egypt and the control group was from apparently healthy population. Written consents were taken from participants in addition to approval from ethical research committee in Ain Shams University. Diagnostic workup and investigations for those patients were done. We found that both the diseased and control groups, although higher in the diseased group, have vitamin D deficiency (59.1%) and (55%) respectively **(p value=0.001)** that reflects the increased incidence of vitamin D deficiency among Egyptian population either healthy or those with neurological diseases. Vitamin D deficiency was also high in neuromuscular disorders (47%) **(P value=0.009)** and cerebrovascular strokes (68%) **(p value=0.006)** that need vitamin D supplementation. More research is still needed to detect the actual relation between vitamin D deficiency and Neurological Disorders.

INTRODUCTION

Vitamin D Deficiency (VDD) has become a worldwide public health problem. It is well known that vitamin D has an established role in skeletal growth, development and its maintenance. Adequate vitamin D status is also important for optimal function of many organs and tissues throughout the body. Deficiency of vitamin D leads to skeletal disorders like rickets in children and osteomalacia in adults. Recent evidence suggest that in addition to skeletal disorders VDD is also responsible for exacerbating various non-communicable diseases such as obesity, hypertension, cardiovascular disease, diabetes mellitus, metabolic syndrome, cancer, neurological including dementia, Parkinson's disease, multiple sclerosis, epilepsy, myopathies and schizophrenia. Due to paucity of scientific evidence on the role of vitamin D in the manifestation of these non-communicable diseases, it becomes necessary to carry out further research and establish the association of VDD with these diseases.

MATERIALS AND METHODS

A case control study was conducted at the neuropsychiatry clinic, Sohag Teaching Hospital. It serves urban and rural areas providing health services to different social classes. We chose one central disorder, the cerebrovascular disorder and one peripheral disorder, the neuromuscular disorder.

The sample consisted of all patients came to the neuropsychiatric clinic during a period of one year from January 2016 till January 2017. We included patients fulfilling the inclusion criteria being 12 years old and more, patients with neuromuscular disorders and cerebrovascular strokes and excluded those with a known cause of VDD such as malabsorption syndromes, resected jejunum and duodenum, parathyroid operations and patients on replacement therapy of Vitamin D. During the study, a total of 88 patients were recruited fulfilling the inclusion criteria of the study and 20 persons were apparently healthy, accepted to share in the study as a control group. They were matched with the patients for age, sex, geographic region and had a negative family history of cerebrovascular or neuromuscular disorders or past history of any disease. All procedures were reviewed by the ethical and research committee, Faculty of Medicine, Ain Shams University. An informed written consent was done by all participants in the study.

For each patient and healthy control, the following had been done: Interviewing Structured Questionnaire, general and neurological examination, Complete blood count, Serum total

Calcium, Kidney Function Tests, Liver Function Tests and Vit D serum level (25 hydroxycholecalciferol).

For patients of the neuromuscular disorders (NMD) group, nerve conduction studies (NCS), electromyography(EMG), Plain X-ray spine and/or long bones (for skeletal deformities) were all done.

For patients of the cerebrovascular group, computed tomography (CT) of the brain and/or magnetic resonance imaging and angiography (MRI/MRA) of the brain were done. Electrocardiogram (ECG), Echocardiography and carotid Doppler were also done. Vitamin D level was considered as severe deficiency if <10 ng/mL, deficiency if 10-19 ng/mL, insufficiency if 20-29 ng/mL, Optimal (healthy) range if 30-50 ng/mL and Intoxication if >125 ng/mL ***[1].*** Data were collected, revised, coded and entered to the Statistical Package for Social Science (IBM SPSS) version 20. Qualitative data were presented as number and percentages. The comparison between two groups with qualitative data were done by using *Chi-square test* and/or *Fisher exact test* which was used when the expected count in any cell was found less than 5. The confidence interval was set to 95% and the margin of error accepted was set to 5%. So, the p-value was considered significant as following, $P > 0.05$: Non-significant, $P < 0.05$: Significant and $P < 0.01$: Highly significant.

RESULTS

In our study, 108 subjects were enrolled (88 patients and 20 controls). Of the patient group (40 patients were with NMD and 48 patients were with Strokes). The mean age of the patient group was (51.73) years with standard deviation 18.7. Of them, 8 (9.1%) were early adolescence, 6 (6.8%) were late adolescence, 3 (3.4%) were early adulthood, 41 (46.6%) were middle adulthood, 26 (29.5) were late adulthood and 4 (4.5%) were older. Forty two (47.7%) of the patients were males and forty six (52.3%) of patients were females (22.7%). Forty five patients (51.1%) were living in rural areas and forty three (48.9%) of patients were living in urban areas. Forty patients were diagnosed with NMD (45.5%) and forty eight (54.5%) were diagnosed with stroke. Thirty nine of the patients (44.3%) had Hypertension (HTN) and thirty one (35.2%) of patients had diabetes mellitus DM. **Table 1** showing the socio-demographic data of the patient group.

Table (1): Socio-demographic data of the patient group

Age Groups		**N**	**%**
Early Adolescence		8	9.1%
Late Adolescence		6	6.8%
Early Adulthood		3	3.4%
Middle Adulthood		41	46.6%
Late Adulthood		26	29.5%
Older		4	4.5%
Sex	**Male**	42	47.7%
	Famale	46	52.3%
marital status	**Single**	20	22.7%
	Married	50	56.8%
	Divorced	3	3.4%
	Widow	15	17%
Residence	**Rural**	45	51.1%
	Urban	43	48.9%
Work	**Employed**	27	30.7%
	Unemployed	61	69.3%

We found that VDD less than 20 ng/ml in the diseased group was (59.1%) versus (55%) in the control group. In the diseased group, 23.9% were with Vitamin D insufficiency (20-29ng/ml) versus (5%) in the control group. Only (13.6%) of the diseased group versus (10%) in control group were with optimal Vitamin D levels (30-50ng/ml). While (3.4%) of the diseased group versus (30%) in the control group were with Vitamin D intoxication (>125 ng/ml) with statistical significant difference of all results of the diseased group compared to the controls **(p value=0.001)**, **Figure. 1 (Vitamin D levels in diseased group), 2(Vitamin D level in the control group) and 3(Vitamin D level in both the diseased group and the Control Group).**

Regarding stroke patient group, we had 48 patients (36 patients with ischemic strokes and 12 patients with hemorrhagic strokes). We found that (68.8%) of stroke patients were with VDD versus (55%) in the control group, (12.5%) had vitamin D insufficiency in stroke patients versus (5%) in the control group, (16.7%) of stroke patients were with optimal vitamin D

levels versus (10%) in the control group. We also found that (2%) of stroke patients had vitamin D intoxication versus (30%) in the control group, with statistically significant difference between vitamin D in stroke patients and the control group with higher percentage of VDD in the stroke group **(p value=0.006).** Vitamin D deficiency was higher in cerebral infarctions (75%) than in hemorrhages (50%) and higher in anterior circulation infarctions (75.9%) than in posterior circulation infarctions (71.4%). It was also higher in large vessel infarctions (78.9%) than in small vessel infarctions (66.7%) and (80%) in the cardioembolic infarctions, **Figure.4 (Vitamin D level in Stroke patients), 5 (Vitamin D in cerebral infarctions and cerebral hemorrhages), 6(Vitamin D level in Large, small vessels and cardioembolic cerebral infarctions), 7(Vitamin D level in anterior circulation and posterior circulation) and 8(Vitamin D level in strokes versus in control Group).** In NMD Group, VDD was found in (47.5%) versus (55%) of the control group, vitamin D insufficiency was found in (37.5%) in NMD versus (5%) in the control group. Optimum vitamin D levels were found in (10%) of NMD versus (5%) in the control group. Vitamin D Deficiency was higher in the neuropathies (55%) than the muscular disorders (41.2%), **Figure 9 (Vitamin D level in NMD), 10(Vitamin D level in NMD versus Controls), 11(Vitamin D level in different NMDs) and 12(Vitamin D level in different NMDs classification).**

VDD was higher in stroke patients (68.8%) more than NMD patients (47.5 %) with significant difference (**P value=0.035**) between the two groups of patients. As regards to VDD within different age groups- there was no significant difference (p-value =0.320), and no significant difference between VDD in urban and rural areas (p value=0.869), but there was a significant difference between males and females as regards to VDD (p value=0.001), **Figure 13 (Vitamin D level in NMD versus Strokes).**

DISCUSSION:

In the present study, results showed that VDD is higher in stroke patients (68.8%) than NMD patients (47.5 %) with significant difference (P value=0.035) between the two groups of diseases. But we didn't find any previous studies that compared these two diseased groups (NMD and Strokes) to each other. VDD was detected frequently in patients suffering from Cerebral infarctions (75%), Neuropathies (55%), Cerebral hemorrhages (50%), Neuromuscular junction (NMJ) disorders (50%), and Myopathies (41.2%), with no statistically significant difference between different diseases (p-value =0.206). These results

are nearly consistent with another study done for VDD detection among different neurological disorders ***[2]*** which revealed that VDD was detected more frequently in patients suffering from Ataxic syndromes (72.7%), Amyotrophic lateral sclerosis (66.7%), spine lesions (63.3%), polyneuropathies (63.0%), and stroke (62.6%). In the present Study, -in regards to VDD within different age groups- there was no significant difference (p-value =0.320), and no significant difference between VDD in urban and rural areas (p value=0.869), but there is a significant difference between males and females as regards to VDD (p value=0.001).Regarding NMD disorders in the present study, there were 40 cases. (2.5%) of them were Anterior Horn Cell (AHC) diseases, (50%) were neuropathies, (5%) were neuromuscular junction disorders and (42.5%) were myopathies. VDD were found in (47.5%) of the NMD versus (55%) of the control group, (37.5%) in NMD versus (5%) in the control group with Vitamin D Insufficiency. (10%) of NMD versus (10%) in the control group with optimum vitamin D. (5%) of NMD versus (30%) of the control group with vitamin D intoxication, with statistically significant difference higher in NMD (p value=0.009). These results are inconsistent with another study that investigated the significance of VDD in the clinic of neuromuscular disease in central Pennsylvania ***[3].*** The researchers found that of 50 blood levels measurements, (70%) were below 20 (deficiency), (6%) borderline, (46%) were between 30 and 40 or more (normal). These differences may be due to fewer patients in our study in comparison to the American one. Or it may be due to the different geographic distribution and its effect of vitamin D level in different societies, habits, climate and lifestyle. However, our study results were consistent with another study that researched the level of vitamin D in patients with neuromuscular disorders and chronic respiratory failure ***[4].*** The study found that low serum 25(OH) D levels are highly prevalent in NMD patients, as (75%) of those patients were with VDD. In our study, we found that Vitamin D Deficiency is higher in the neuropathies (55%) than the muscular disorders (41.2%). In NMJ disorders Vitamin D deficiency percentage (50%) is equal to optimum Vitamin D (50%) in neuromuscular junction disorders. In AHC diseases, (100%) were with vitamin D insufficiency. These findings are inconsistent with a recent Greek study ***[5]*** that investigated the level of Vitamin D in neuromuscular disorders in a control Study on 30 healthy controls and 30 patients of Myasthenia Gravis(MG) and Autoimmune Polyneuropathies with supplementation of Vitamin D3. It discovered that Vitamin D Deficiency was found in all Greek patient groups and healthy controls and that levels of vitamin D were higher in MG patients with and without vitamin D supplementation, compared to healthy controls. Whereas chronic Idiopathic Demyelinating polyneuropathy/

Gullian Barre Syndrome (CIDP/GBS) patients had levels similar to controls. These differences in the results from our side may be due to a different number of patients in both studies, the different geographical distribution or the different design of both studies in regards to classifications of the NMD. Also, we couldn't compare MG patients alone with the control group because of the lower number of MG patients in our study. But we compared the whole NMD with controls as mentioned above. Regarding stroke patient group in our study, we had 48 patients (36 patients with ischemic strokes and 12 patients with hemorrhagic strokes). We found that (68.8%) of stroke patients were with VDD versus (55%) in the control group, (12.5%) had vitamin D insufficiency in stroke patients versus (5%) in the control group, (16.7%) of stroke patients were with optimal vitamin D levels versus (10%) in the control group. We also found that (2%) of stroke patients had vitamin D intoxication versus (30%) in the control group, with statistically significant difference between vitamin D in stroke patients and the control group with higher percentage of VDD in the stroke group (p value=0.006). These results were consistent with another study ***[6]*** that was done on 87 hemiplegic stroke patients (42 outpatients and 45 inpatients) and 28 control subjects. It concluded that the difference in serum 25-OHD between the two patient groups was statistically significant but with higher percentages than ours, as 95% of the outpatients and 98% of the hospitalized patients had deficient or insufficient serum levels of 25-OHD. It was surprising to discover that 7 outpatients and 21 inpatients had serum 25-OHD levels that were consistent with osteomalacia (≤5 ng/mL).The results were in line with an Indian study ***[7]*** which was done on 250 of stroke patients. The results were consistent with ours as they found that VDD were observed in (48.8%) stroke patients versus (31.6%) controls with statistically significant difference (P=0.001). The results of our study were also consistent with the meta-analysis***[8]*** done on 10,170 individuals from the general population at the Copenhagen City Heart Study. During 21 years of follow-up, 1,256 and 164 persons developed ischemic and hemorrhagic stroke, respectively. It concluded that stepwise decreasing plasma 25-hydroxyvitamin D concentrations were associated with stepwise increasing risk of ischemic stroke. However, the results of our study were inconsistent with those found in a recent study ***[9]*** that researched the relation between serum Vitamin D levels and body antioxidant status in ischemic stroke patients. It was a case-control study on 36 patients with ischemic stroke patients and 36 matched subjects as controls. It concluded that severe Vitamin D deficiency was seen only in 30% of the patients versus 11% of the controls. Despite the smaller percentage of VDD, it is still with statistically significant difference (P value < 0.05). These differences between the two studies are maybe due to the fewer number of our controls, or

perhaps due to the different design of the mentioned study in regards to antioxidants intake. Our study results were also inconsistent with the Indian study ***[7]*** done to investigate the status of VDD among stroke patients on 73 cases and 70 controls. It found that only 27.4% of cases and 34.3% of controls were vitamin D sufficient and there was no significant difference among cases and controls in vitamin D status. In the current study, we found that Vitamin D deficiency is higher in cerebral infarctions (75%) than in hemorrhages (50%) and higher in Anterior circulation infarctions (75.9%) than in posterior circulation infarctions (71.4%). it was also higher in large vessels infarctions (78.9%) than in small vessels infarctions (66.7%) and higher in (80%) of the cardioembolic infarctions. These results were consistent but with higher percentages than an Indian study ***[10]*** done on 250 stroke patients. Among them, serum 25-hydroxyvitamin D deficiency was found in (54.9%) of patients with large artery atherosclerosis, (44.4%) in small artery diseases, (54%) in cardioembolic stroke, 42.8% in stroke of other determined etiology and 40.4% in stroke of undetermined etiology. The study concluded that 25-hydroxyvitamin D deficiency had an independent association with ischemic stroke and the association was strongest in large artery atherosclerosis and cardioembolic stroke. In Aswan University, in Upper Egypt, a comparative study ***[11]*** between risk factors and stroke type was performed. It was a case control observational perspective study conducted on fifty (25 patients with intracerebral hemorrhage and 25 patients with ischemic infarction). ***Altony and colleagues [11]***announced at the 18th Cairo National Conference: 84% and 76% of patients with ischemic Infarction and intracerebral hemorrhage respectively had insufficient vitamin D Levels (<50 Nmol/L), with no statistically significant difference between the two groups of patients. No association between vitamin D levels, severity of stroke and functional outcome in patients with ischemic infarctions was observed. These different results from ours are perhaps due to the different numbers of our patient groups as 36 patients were with cerebral infarctions and 12 patients with hemorrhagic strokes and maybe also due to the different points of view in comparison between studied groups in both studies. In ours, we compared the VDD in the strokes (either infarctions and hemorrhages) to the control group and found that there was a significant difference (p-value = 0.009). We also found that VDD in infarction strokes was (75%) and in cerebral hemorrhages was (50%). Also we studied the VDD in the subtypes of the ischemic strokes and we found that VDD is (75.9%) in anterior circulation infarctions, (71.4%) in posterior circulation infarctions, (78.9%) in large vessel infarctions, (66.7%) in small vessel infarctions and (80%) in cardioembolic infarctions. However, in the other study in Aswan, VDD was compared in infarctions to cerebral hemorrhages. Other studies researched vitamin

D level in stroke patients from other perspectives. They studied the association between low vitamin D levels and brain infarct volume and the outcomes of ischemic patients. They found that low Vitamin D level is associated with larger brain infarct volume and worse outcomes in patients with ischemic stroke. They also found that patients with a low vitamin D level had twice the infarct volume of those with normal levels, about 17 vs 8 mL (P value = .01). The relationship was similar in several stroke subtypes, with a significant association for lacunar strokes (P = .001) but a non-significant trend for non-lacunar strokes (P = .072) ***[12].*** On the other hand, other studies have researched the relationship between stroke mortality and vitamin D deficiency and found that Stroke mortality was 3X worse among seniors with less than 26 ng of vitamin D ***[13].*** There are some limitations in our study, such as the fewer number of cases and the fewer number of controls in comparison to the numbers of the diseased group. Also, we didn't study the effect of the infarct size in stroke patients. We also acknowledge it would have been more conclusive if we performed some genetic testing and muscle biopsy in patients with NMD. But still, we have the advantage of having a new study in our society to investigate the frequency of VDD in new diseases (NMD and strokes). This, as far as we know, had never been studied in Sohag Governorate before.

CONCLUSION

We studied the frequency of Vitamin D deficiency among patients with neuromuscular and cerebrovascular disorders in one of the Egyptian Teaching Hospitals in upper Egypt. We found that both the diseased and control groups, although higher in the diseased group, have vitamin D deficiency that reflects the increased incidence of vitamin D deficiency among Egyptian population. Vitamin D deficiency was higher in cerebrovascular strokes, more than neuromuscular disorders that need vitamin D supplementation. More research is still needed to detect the actual relation between vitamin D deficiency and Neurological Disorders.

A) List of abbreviation:

Abb.	Full term
AHC	Anterior Horn Cell
CBC	Complete Blood Count
CIDP	Chronic Idiopathic Demyelinating Polyneuropathy
CNS	Central Nervous System
CT	Computed Tomography
CVS	Cerebrovascular Strokes
DM	Diabetes Mellitus
EMG	Electro Myogram
ECG	Electrocardiogram
GBS	Gullian Barre Syndrome
HTN	Hypertension
MG	Myasthenia Gravis
Ml	Millimeter
MRI	Magnetic Resonance Imaging
MRA	Magnetic Resonance Angiography
NCS	Nerve Conduction Study
Ng	Nanogram
NMD	Neuromuscular Disorders
NMJ	Neuromuscular Junction
OH (D)	Hydroxyvitamin D
SD	Standard Deviation
VDD	Vitamin D Deficiency
VitD	Vitamin D
VS	Versus

A) Ethics approval and consent to participate :

Statement on ethics approval and consent:

The study was conducted after approval through a written consent and after receiving the approval of the scientific ethical committee of Faculty of Medicine- ain Shams University.

Name of ethics committee and number: Ethical Committee of Faculty of Medicine, Ain Shams University.

B) Consent for publication: not applicable

C) Availability of Data and material: All data present in this manuscript can be found with any one of the four authors, can be demanded by their contact information and we approve sharing these data.

D) Competing Interests: Authors don't have competing interests either financial or non-financial.

E) Funding: The fund of all stages of the study are author's own fund.

F) Authors contributions :

Prof Nagia Fahmy choose the subject, revised the whole work and shared in writing the manuscript, Dr. May Abdellah examined the patients, collected the samples and shared in writing the manuscript, Dr. Maha Nada revised the work and statistics and Dr. Magdy Mostafa revised the work and statistics.

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