To Determine the Relationship between Migraine and Vitamin D Levels in Patients Presenting in Tertiary Care Hospital in Northern India

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ABSTRACT

Introduction: Vitamin D deficiency is common across all age groups. Serum 25-hydroxyvitamin D deficiency as risk factor for migraine has documented in recent reports and it may contribute to the disease and its prevention. Migraine is the second most common cause of headache and is the one causing maximum disability. Migraine is neurological disorder which is progressive and chronic in nature. The incidence is more common in women than men. Aims and Objectives: To study of relationship between Migraine and Vitamin D level in patients clinically diagnosed cases of migraine presenting in tertiary care hospital.

Material and Methods: It is a Prospective observational study. Those patients that were willing to participate in the study with the clinical diagnosis of migraine were enrolled in study. The severity of migraine was judged using the pre-validated Migraine Disability Assessment Score (MIDAS) Questionnaire

Results: Out of 50 patients of the migraine, 27 (54%) were female and 23 (46%) were male with the mean age was 41.38±15.46 (age range between 20 to 80 years). The severity of vitamin D was divided into severe deficiency, deficiency, insufficiency and sufficiency. Cases when compared to controls, severe deficiency was noted in 8 vs 1 whereas as deficiency as seen in 21 Vs 6 respectively. Insufficiency was more seen in controls as compared to cases i.e. 29 Vs 15. 14 controls had normal Vitamin D Levels as compared to only 6 in cases group. This overall difference was statistically significant p<0.0001. The mean value of Vitamin D in cases was significantly lower when compared to the age and sex matched control group i.e. 19.76 ± 8.78 Vs 26.6 ± 6.52, p<0.0001.

Conclusion: Vitamin D levels are significantly lower in patients of migraine when compared to controls. Better, larger randomized control trials are required to see if treatment for Vitamin D deficiency either decreases the symptom or improves the diseases.

Keywords: Migraine, Vitamin D Levels

INTRODUCTION

Headache is one of the commonest symptoms treated by a physician in a routine outpatient clinic and is seen in a wide variety of neurological disorders. World Health Organization categorizes headache disorders into the top 10 disabling conditions among two gender and into the five most disabling condition amongst women.[1] Migraine is defined as a common hereditary chronic neurovascular disorder, resulting from dysfunction of the autonomic nervous system.

In few patients, it is associated with nausea or vomiting along with phonophobia and photophobia.[2] The incidence is 18% among women and 6% in men and maximum incidence is seen in ages between 25 and 55.[3]

In migraine with aura, visual disturbances accounts maximally for producing transient neurologic manifestations. It is maximally observed that these are initiated with positive phenomena such as stars, spark photopsia, complex geometrical patterns, and fortification spectra, that may leave their wake negative phenomena such as scotoma or hemianopia. The onset and progression of symptoms are usually slow. Visual disturbances are experienced at times like micropsia or dysmetropsia. The second most common symptom accounts for is somatosensory complaints mainly over hand and lower face in the form of tingling and numbness. Rarely, it is seen that it can present with loss of voice, weakness or clumsiness of one side of the body. The progression of symptoms are slow marching. The variations of symptoms tells us about the spread of neurologic dysfunction from the occipital cortex into the regions of the temporal or parietal lobes. The aura resolves nearly in nearly 30 minutes and is followed after a brief pause of normality by headache, nausea and or vomiting, photophobia, and phonophobia. Prior to the onset of headache patient can ex-perience some behavioural changes. As soon as the attack subsides, within the a period of 24 hours patient may experience spectrum of behavioural changes ranging from depression to exhilaration.[4]

Management with triptans was an advancement in the treatment of migraine headache, but patients must abide the symptoms of migraine until the medica-tions shows its

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effects. The side effects of triptans are drowsiness, weight gain, and hair loss and the contraindications are in patients with coronary artery disease or stroke, or with pregnancy.[5]

Vitamin D (1,25 hydroxy vitamin D) is a steroid derivative which is synthesized by the help of ultraviolet radiation by conversion of 7-dehydrocholesterol present in subcutaneous fat with the half-life of nearly 2-3 weeks. The absorption of Vitamin D is hampered by use of sunscreens which ultimately results in vitamin D deficiency and its level are best measured by measuring the level of 25-hydroxy vitamin D. Normal range of vitamin D is 75 - 150 nmol/l.

Certain observational studies have revealed low serum vitamin D levels in patients with headache.[4] and high prevalence of vitamin D insufficiency in patients having myalgia and depression[5] (two most common comorbidities associated with headache disorders) and increased level of vitamin D receptor and vitamin D binding protein in the hypothalamus is conclusive of association between vitamin D and headache.[6] A major chunk of studies also revealed both positive and negative correlation with the occurrence of migraine. However, it was also found that severity of migraine and its association with vitamin D is not studied well especially using the standard methodology like Migraine Disability Assessment Score (MIDAS) Questionnaire. Hence we planed to conduct a study in our setting where the majority of patients are from rural background and field workers, having enough exposure to sunlight. These patients are less likely to have Vitamin D deficiency. This study will help us in proper utilization of the resources and will avoid unnecessary investigations in the patients.

MATERIAL AND METHODS

It was a Prospective observational study, conducted in a tertiary care teaching Institute in Mullana village of Ambala district in north India. The department of medicine receives a high percentage of neurology patients consisting of patients of neuropathy, seizures, Parkinson's disease, stroke and headache due to different pathologies like migraine, Chronic daily headache and tension headache. The department also runs a specialty clinic of neurology once a week. We enrolled about 50 patients of clinically diagnosed cases of migraine as per the below mentioned simplified diagnostic criteria and an equal number of age and sex matched controls.

Diagnostic Criteria for Migraine

Migraine is defined as "an episodic headache associated with certain features such as sensitivity to light, sound, or movement nausea and vomiting often accompany the headache".[7]

Simplified Diagnostic criteria for Migraine

Repeated attacks of headache lasting 4-72 hrs in patients with a normal physical examination, no other reasonable cause for the headache and at least 2 of the following features-
• unilateral pain,
• throbbing pain,
• aggravation by movement,
• moderate or severe in intensity,

Plus at least 1 feature from-
• Nausea/vomiting
• Photophobia/Phonophobia.

All consecutive outpatients presenting in the Medicine OPD and Neurology clinic with primary history of headache were screened for migraine as per the above-mentioned diagnostic criteria's. Those patients that were willing to participate in the study with the clinical diagnosis of migraine were enrolled in study. For each enrolled patient demographic profile with detailed history with respect to duration, type and medication for headache was enquired and noted. Associated symptoms like nausea, vomiting, photophobia, lightheadedness, scalp tenderness, visual disturbance, paresthesia's, vertigo, photopsia, alteration in level of consciousness, syncope, seizures and focal deficit were collected. The severity of migraine was judged using the pre-validated Migraine Disability Assessment Score (MIDAS) Questionnaire.

According to the questionnaire the disability was graded into four grades with Grade IV being most severe and Grade I signifying mild severity. All the patients were evaluated for serum Vitamin D levels at the time of diagnosis. The levels of Vitamin D was graded into Severe Deficiency (< 10 ng/ml), Deficiency (10-20ng/ml), Insufficiency (20 – 29ng/ml) and Sufficient (>29ng/ml).[8] CT/ MRI or EEG was done where the diagnosis of migraine was doubtful or patients had associated red flag signs. They were treated as per the standard treatment regime as per the discretion of the physician. For each enrolled patient age and sex matched control without any history of headache or consumption of Vitamin D supplementation in previous 6 months were taken. The control subjects were subjected to Vitamin D level estimation.

STATISTICAL ANALYSIS

All variables from questionnaire were entered into Microsoft excel sheet. Statistical data analysis was done using Statistical software. Data was summarized in the form of proportions and frequent tables for categorical variables. Continuous variables were expressed as means ± standard deviation and were compared using Student t-test. Categorical values were expressed in absolute and relative frequencies, and were analysed using $\chi 2$ test. P ≤ 0.05 was considered statistically significant.

RESULTS

A total of 50 subjects with primary diagnosis of Migraine were enrolled in the study as per the inclusion criteria. Equal number of age and sex matched controls were taken. The mean age of both cases and controls was 41.38 SD ± 15.46. Majority of patients were young and between the age group of 20 to 30 years (table-1).

In this study both case and control groups, 54% were females and 46% were males which indicates that migraine is more common among females. We studied the symptomatology of the cases and it was seen that 38 (76%) patients presented with unilateral whereas the rest had bilateral headache (24%).78% of patients gave history of intolerance to light

whereas phonophobia was noted in 74% of patients. Presence of Nausea was the commonest symptom present in 82% of patients however only 50% of patients experienced vomiting and 19 cases present with aura.

When we compared the severity of headache as per the MIDAS Q scoring system it was seen no patient had a score < 5, whereas 40% of patients were in MIDAS 2 Grade with a mean MIDAS score of 7.5. Severe headache i.e. MIDAS 3 and MIDAS 4 grade was seen in 32% and 28% of patients respectively with a mean MIDAS score of 15.25 and 22.07 respectively (table-2).

Vitamin D deficiency was checked in all the cases and it was found to be deficient in 88% of cases. Only 12% in the case arm had normal Vitamin D levels. Out of 50 cases, 8 (16%) cases were severely vitamin D deficient (<10ng/ml), 21 (42%) were vitamin D deficient (10-20ng/ml) and 15 (30%) of them had vitamin D insufficiency (20-29ng/ml). Only 6 (12%) had normal vitamin D levels (table-3).

Severe deficiency was seen in 16% of cases as compared to 2% in controls whereas deficiency was seen in 42% and 12% of cases and controls respectively. This difference was statistically significant with P<0.0001. The mean value of Vitamin D in cases was significantly lower when compared to the age and sex matched control group i.e. 19.76 ± 8.78 Vs 26.6 ± 6.52, p<0.0001, proving that Vitamin D level may plays a significant role in the pathophysiology of migraine. Severity vitamin D levels were compared with the MIDAS Q grading. As per MIDAS Q grading 50% and 44% of patients of MIDAS II and III grade were in the deficient range of Vitamin D levels respectively. However, majority of grade IV subjects (43%) had insufficient levels of Vitamin D as per the severity classification. However, this difference was not statistically significant with p value was found out to be 0.701 which was not significant (table-4,5,6).

The mean Vitamin D level for Grade II, III and IV MIDAS was found to be 17.54±8.19, 21.07±9.05 and 21.44± 9.25 respectively. This difference in the level of Vitamin D was found to be insignificant with p value of 0.349. The mean of vitamin D was compared with the presence and absence of aura. In the presence of aura the mean of vitamin D was 18.05±8.05 whereas in the absence of aura the mean of vitamin D was 20.8±9.17. The mean of vitamin D was more in the absence of aura but was not statistically significant with p value was 0.285 (table-7).

DISCUSSION

The plethora of recent scientific reports highlights a wide sphere of physiological effects mediated by vitamin D. This multifunctionality has been attributed to the elicitation of physiological responses mediated by Vitamin D in ≥36 cell types that express its specific receptor, Vitamin D receptor.[8] There have been many new advances in the knowledge of

		Groups		Total
		Case (N=50)	Control (N = 50)	
Age	20-30	32%	32%	32.00%
	31-40	18%	18%	18.00%
	41-50	22%	22%	22.00%
	51-60	18%	18%	18.00%
	>60	10%	10%	10.00%
Total		100.00%	100.00%	100.00%

Table-1: Distribution of cases and controls according of the age

Grades	Number of patients	Mean ± standard deviation
MIDAS 2	20 (40%)	7.5
MIDAS 3	16 (32%)	15.25
MIDAS 4	14 (28%)	22.07

Table-2: Severity of headache according to midas score in patients of migraine

Severity		Total
VIT D	Severe deficiency	8 (16.00%)
	Deficiency	21 (42.00%)
	Insufficiency	15 (30.00%)
	Sufficiency	6 (12.00%)
Total		50 (100.00%)

Table-3: Distribution of vitamin d deficiency among cases

		Groups		Total	P value
		Case	Control		
VIT D	Severe deficiency	8 (16%)	1 (2%)	9.00%	<.0001
	Deficiency	21 (42%)	6 (12%)	27.00%	
	Insufficiency	15 (30%)	29 (58%)	44.00%	
	Sufficient	6 (12%)	14 (28%)	20.00%	
Total		50(100.00%)	50(100.00%)	100.00%	

Table-4: Showing comparision of vitamin d levels between cases and controls.

VIT D	Cases	Controls	
Sample size	50	50	<0.0001
Mean ± SD	19.76 ± 8.78	26.6 ± 6.52	
Median	18.84	26.15	
Min-Max	5.65-37.65	7.65-42.6	
Inter quartile Range	13.350-26.540	23.130-30.760	

Table-5: Relationship of vitamin d in cases and controls group

Severity		MIDAS Q			P value
		Grade II	Grade III	Grade IV	
VIT D	Severe deficiency (n=8)	4 (20%)	2 (13%)	2 (14%)	0.701
	Deficiency (n=21)	10 (50%)	7 (44%)	4 (29%)	
	Insufficiency (n=15)	5 (25%)	4 (25%)	6 (43%)	
	Sufficient (n=6)	1 (5%)	3 (19%)	2 (14%)	
Total (n=50)		20 (100.00%)	16 (100.00%)	14 (100.00%)	

Table-6: Showing comparison of midas questionnaire grading with vitamin D levels in cases.

	MIDAS Q			P value
	Grade II	Grade III	Grade IV	
VIT D	17.54	21.07	21.44	0.349

Table-7: MIDAS questionnaire with mean value of vitamin D levels

the biology of vitamin D that include its effects on diverse and major health outcomes like cancer, autoimmune and cardiovascular diseases. However, despite the mounting awareness of the beneficial aspects of vitamin D, there is a pandemic of Vitamin D deficiency.

This study was conducted to study the levels of Vitamin D in migraine patients. This study is a case-control study with 50 patients of migraine acting as cases and 50 age and sex-matched healthy individuals acting as controls. On the basis of the defined cut off of 20 ng/ml for Vitamin D deficiency,[9,10,11] we found 56% of the control population to be Vitamin D deficient.

The mean Vitamin D value of the cases group with migraine was 19.76 ± 8.78 ng/dl with a median value of 18.84 ng/dl. The range of vitamin D levels in cases was from 5.65 ng/ dl to 37.65 ng/dl. The mean value of the control group (without migraine) was 26.6 ± 6.52 ng/dl and a median of 26.15 ng /dl. The range of vitamin D levels in control group was 7.65 to 42.6 ng/dl. The p value between the two groups was less than 0.0001, which is statistically significant, showing a correlation between decreased levels of vitamin D with migraine.

All other parameters like haemoglobin, total leucocyte count, ESR, creatinine, urea, SGOT & SGPT were similar in both cases and control groups with p-value >0.05, thus being insignificant.

Strengths and limitation of the study
Our study, as per our knowledge is the first of its kind which has compared the Vitamin D levels with the MIDAS grades of Migraine. This was a unique study which opens avenues for further larger randomized control studies. The study was a single centered study thus avoiding the variability in the selection of patients. Majority of the patients in the study were from rural background who generally have an adequate exposure of sunlight. However still the vitamin D deficiency was seen in more than 50% of patients. The study had some limitations too. The sample size of the study group was small as compared to the incidence of the Migraine in the general population.

This was due to the availability of limited resources as none of the patients of Control or Case groups were charged for the Vitamin D Levels. The study was an open study i.e. the investigator was not blinded. The results of the study cannot confirm the definitive correlation between Vitamin D and Migraine as the patients were not treated for the deficiency to see for the response for decrease in the MIDAS score on follow or post therapy.

Thus we want to stress that Vitamin D has been shown to exert multiple beneficial health effects beyond its proposed role in the prevention and treatment of migraine. Hence, it could be hypothesized that a widely introduced Vitamin D treatment might be beneficial for many diseases beyond migraine. This should encourage a goal in public health care strategies to fight against Vitamin D deficiency.

CONCLUSION

Fortunately, both migraine and Vitamin D deficiency are controllable and treatable parameters, hence we suggest that effective healthcare programs should be organized countrywide for the monitoring and management of the serum levels of Vitamin D and migraine. Random clinical trials should also focus on supplementation of Vitamin D in subjects with severe Vitamin D deficiency and particularly those with a background of migraine.

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