Relationship among cognitive function, depression, and vitamin D in a sample of Egyptian patients with migraine

Manal H. Maabady[a], Rasha S. Elattar[a], Asmaa M. Elaidy[b], Salwa I. Elshennawy[c]

Background Migraine is the second most common cause of headache worldwide. Recently, vitamin D deficiency has been considered as a global health problem. Cognitive impairment and depression are common comorbidities with both migraine and vitamin D deficiency. Some studies have shown relationship between vitamin D deficiency and migraine; however, the available evidence on association among vitamin D, migraine, and those comorbidities is limited.

Objective To study the relation between vitamin D and migraine and to explore its relation to depression and cognitive impairment as comorbidities of migraine.

Patients and methods This was a cross-sectional comparative case–control study. A total of 30 patients with migraine aged 18–41 years were included along with 30 controls, who were age and sex matched. All patients were assessed for frequency, duration of migraine attacks, and Migraine Disability Assessment Scale (MDAS). All patients with chronic migraine were not on prophylactic treatment. Moreover, patients and control were exposed to Hamilton Depression Rating scale (HAM-D) and Montreal Cognitive Assessment (MoCA) to assess depression and cognition, respectively. Serum vitamin D level was also measured.

Results Serum vitamin D was significantly decreased in migraineurs with negative correlation to duration of disease and frequency of attacks; however, it was not significant to cognitive impairment or depression. MoCA and HAM-D were significantly affected in patients with migraine than control with significant decline in chronic form of migraine; however, there was no significant difference between migraine with aura or without. MoCA and HAM-D were also related to MDAS but not to vitamin D.

Conclusion Serum vitamin D is deficient in migraineurs and was related to frequency of attacks but not to the severity of migraine, associated depression, or cognitive impairment. Cognitive impairment and depression were explored in migraineurs and related to MDAS. Cognitive impairment is related to both migraine with aura or without aura, and patients with chronic migraine are affected more than those with episodic migraine.

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Departments of, [a]Neurology, [b]Psychiatry, [c]Clinical Pathology, Faculty of Medicine for Girls, Al-Azhar University, Cairo, Egypt

Correspondence to Rasha Sobhy El Attar, MD of Neurology, Lecturer of Neurology Al Azhar University.
e-mail: drrashaelattar@gmail.com

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Introduction

Population studies on migraine report prevalence rates between 2.6 and 21.7%, with an average of ~12% [1]. Migraine is considered a common disorder, with an average prevalence of 20% in women and 9% in men [2]. Migraine headache is the sixth highest cause of disability worldwide [3]. In past years, vitamin D deficiency has been known as a global public health problem [4]. It has been associated with severe headache pain and is considered a potential adjuvant in the management of migraine [5].

Vitamin D deficiency was associated with cognitive decline, poorer cognitive performance, and a faster rate of cognitive decline [6]. The serum level of vitamin D is related to sun exposure, dietary intake, and genetic components [7].

Hypovitaminosis D is quite prevalent in patients with cognitive difficulties, with estimates ranging from 70 to 90%. Similarly, low vitamin D is prevalent in other pathologies such as depression and major neurocognitive disorder [8].

Many studies found migraineurs performing worse in a task of sustained attention and processing speed, suggesting an impairment in executive functions and attention [9]. Prevalent comorbidities (e.g. depression and anxiety) can also contribute to but cannot alone account for the cognitive impairment in migraineurs [10].

It has been suggested that depressive and anxious symptoms were strongly associated with severe migraine-related disability [11]. Several studies have found that individuals with a history of migraine

generally have a 1.4–6 times higher risk of developing depression than those without a history of migraine [12].

Affective-motivational brain regions that have been commonly identified as having abnormal function or structure in migraine studies include anterior cingulate cortex, anterior insula, prefrontal cortex, hippocampus, and amygdala [13]. Moreover, these regions are affected in both depression and cognitive impairment [14].

Vitamin D has a key element in development of depression and cognitive impairment and also has begun to be studied as a prophylactic treatment of migraine [15]. This study was conducted to explore association between vitamin D and migraine as a risk factor for depression and cognitive impairment and could be used as an adjuvant treatment for decreasing migraine severity and associated comorbidities.

Patients and methods

This is a cross-sectional case–control study. The ethics committee of the university hospital institute approved the study. An informed written consent was obtained from all participants before their enrollment into the study. It included two groups. The patient group included 30 Egyptian patients with migraine from the Neurology outpatient clinic of Al-Zahraa University Hospital, Al-Azhar University, Cairo, Egypt, from January 2017 to July 2017. The patients were between 18 and 40 years of age who were diagnosed as having migraine with or without aura and chronic migraine according to the third edition of the International Classification of Headache Disorders. Patients taking prophylactic treatment of migraine, secondary headaches, associated any systemic disease that may affect cognition such as diabetes or hypertension, or those with other neuropsychiatric disorders were excluded. The control group included 30 apparently normal volunteers who were age, sex, education, and social standard matched with the participants, with no history of migraine, no systemic diseases, or no neurological diseases. All participants were kept fully informed during the clinical procedures. Each interview began with the explanation of the study objectives to all participants and that their information was to be used only for scientific purposes. An informed consent was obtained from all participants in the study before conducting the interviews. All patients and control cases were subjected to a semi-structured interview that gathered demographic data. For patient group, migraine was diagnosed by a clinician based on clinical history and neurological examination; monthly frequency of attacks and headache duration in years were also gathered. Serum vitamin D was measured. The 25-hydroxyvitamin D [25(OH)D] was chosen as the clinical measure of vitamin D status for participants because of its widespread clinical application, standardized ranges, and testing protocol. The immunodiagnostic ELISA kit was used for the quantitative determination of the vitamin D in serum of all patients and controls. Vitamin D status is readily assessed by measuring serum 25(OH)D. Reference value of 25(OH)D was considered as follows: deficient: less than or equal to 20 ng/ml, insufficient: 21–29 ng/ml, and sufficient: more than 30 ng/ml. The following tools of assessment were used. First, Hamilton Depression Rating Scale (HAM-D) was used to rate the severity of depression. Second, Montreal Cognitive Assessment (MoCA) was used to assess cognition. Finally, Migraine Disability Assessment Scale (MDAS) was used to assess migraine severity in the patient group.

Statistical analysis

Data were fed to the computer and analyzed using IBM SPSS software package, version 20.0. (IBM Corp., Armonk, New York, USA). The Kolmogorov–Smirnov, Shapiro, and D'agstino tests were used to verify the normality of distribution of variables. Comparisons between groups for categorical variables were assessed using χ^2 test (Fisher or Monte Carlo). Student's *t* test was used to compare two groups for normally distributed quantitative variables. Mann–Whitney test was used to compare between two groups for abnormally distributed quantitative variables, whereas analysis of variance was used for comparing the four studied groups, and Kruskal–Wallis test was used to compare different groups for abnormally distributed quantitative variables. Spearman's coefficient was used to correlate between quantitative variables. Significance of the obtained results was judged at the 5% level. *P* value less than 0.05 was considered significant.

Results

The current study was done on 30 Egyptian patients with migraine and 30 controls.

Most cases were female, representing 60% in the patient group and 76.7% in the control group. The median age was 29.7±7.1 years in the patient group and 32.1±5.5 years in the control group. The mean HAM-D was 10.3±6.1 in the case group compared with 2.27

±1 in the control group. Most patients showed moderate degree of depression (40%), whereas 13.3% each showed mild and severe degree of depression.

The mean MoCA was 23.9±2.4 in the patient group compared with 28.6±0.8 in the control group, with 22 (73.3%) patients with MoCA less than 26. The mean vitamin D level was 16.8±7.5 in the patient group compared with 25±2.9 in the control group. In the patient group, the mean duration of illness was 4.7±2.6 years, and the mean frequency of episodes was 6.1±2.7. Most patients were without aura (73.3%), and most patients had episodic type of migraine (60%). According to MDAS, most patients had moderate degree of severity (40%) (Tables 1–3).

As shown in Table 4, the correlation conducted in the current study revealed a highly significant relation between severity of migraine and severity of depression. Moreover, the disability is significant in chronic migraine.

As shown in Table 5, the correlation conducted between MoCA and different parameters revealed that there was a high significant difference between MoCA, severity of migraine, and severity of depression. There was also a high significant correlation between MoCA and type of migraine (chronic migraine); however, there was no significant correlation regarding presence or absence of migraine aura or serum level of vitamin D.

As shown in Table 6, the correlation conducted between vitamin D and different parameters showed statistically significant relation between frequency of migraine episodes and duration of illness.

Discussion

Migraine is a common headache disorder with an average prevalence of 20% in women and 9% in men. Migraine headache is the third most prevalent disorder and the sixth highest specific cause of disability worldwide [16]. Vitamin D has a key element in development of depression and cognitive impairment and has also begun to be studied as a prophylactic treatment of migraine [15].

Cognitive dysfunction has recently gained attention as a significant problem among those with migraine. Although cognitive symptoms are not considered among the core symptomatology of migraine, many migraineurs often complain cognitive decline [17]. Affective-motivational brain regions that have been commonly identified as having abnormal function or structure in migraine studies include anterior cingulate cortex, anterior insula, prefrontal cortex, hippocampus, and amygdala [13]. Moreover, these regions are affected in both depression and cognitive impairment [14].

The burden of migraine is compounded by other cooccurring disorders, including psychiatric disorders and vitamin D deficiency .Thus, it is important to identify manageable comorbidities for effective treatment of migraine [18].

There is contradictory evidence of the association between migraine and cognitive impairment. Several

Table 2 Demographical data of patients with migraine

Descriptive data of patients with migraine	*n* (%)
Duration	
Median (minimum–maximum)	4 (1–10)
Mean± SD	4.7±2.6
Frequency	
Median (minimum–maximum)	5 (1–12)
Mean ± SD	6.1±2.7
MDAS	
No disability	2 (6.7)
Mild	8 (26.7)
Moderate	12 (40)
Severe	8 (26.7)
Type of migraine	
Migraine without aura	22 (73.3)
Migraine with aura	8 (26.7)
Type of MIG2	
Episodic	18 (60)
CH	12 (40)

MDAS, Migraine Disability Assessment Scale.

Table 1 Demographical data

	Cases (*N*=30)	Control (*N*=30)	Test of significance	*P*
Age (years)				
Median (minimum–maximum)	29 (18–39)	31 (23–40)	t=1.422	0.160
Mean±SD	29.7±7.1	32.1±5.5		
Sex [*n* (%)]				
Male	12 (40)	7 (23.3%)	χ^2=1.926	0.165
Female	18 (60)	23 (76.7)		

Table 3 Comparison of Hamilton Depression Rating scale, Montreal Cognitive Assessment, and vitamin D among the total sample

HAM-D [n (%)]				
Normal	10 (33.3)	30 (100)	χ^2=31.301*	<0.001*
Mild	4 (13.3)	0 (0)		
Moderate	12 (40)	0 (0)		
Severe	4 (13.3)	0 (0)		
Median (minimum–Maximum)	13 (1–21)	2 (1–4)	*U*=106.0*	<0.001*
Mean±SD MoCA	10.3±6.1	2.27±1		
<26	22 (73.3)	0 (0)	χ^2=40.000*	<0.001*
≥26	8 (26.7)	30 (100)		
Mean± SD	23.9±2.4	28.6±0.8		
Vitamin D				
Median (minimum–maximum)	15.5 (5.1–27.8)	25.4 (20.2 –30.5)	*U*=185.0*	<0.001*
Mean±SD	16.8±7.5	25±2.9		

χ^2, χ^2 test; HAM-D, Hamilton Depression Rating scale; MoCA, Montreal Cognitive Assessment; *t*, Student's *t* test; *U*, Mann–Whitney test. *P*: *P* value for comparison between the two studied groups. *Statistically significant at *P* value less than or equal to 0.05.

Table 4 Relation between Migraine Disability Assessment Scale and different parameter in the case group (*N*=30)

	MDAS				Test of significance	*P*
	No disability (*N*=2)	Mild (*N*=8)	Moderate (*N*=12)	Severe (*N*=8)		
HAM-D [*n* (%)]						
Normal	2 (100)	8 (100)	0 (0)	0 (0)	χ^2=35.301*	<0.001*
Mild	0 (0)	0 (0)	4 (33.3)	0 (0)		
Moderate	0 (0)	0 (0)	8 (66.7)	4 (50)		
Severe	0 (0)	0 (0)	0 (0)	4 (50)		
Type of migraine [*n* (%)]						
Migraine without aura	2 (100)	6 (75)	10 (83.3)	4 (50)	χ^2=3.071	0.368
Migraine with aura	0 (0)	2 (25)	2 (16.7)	4 (50)		
Type of migraine						
Episodic	2 (100)	8 (100)	6 (50)	2 (25)	χ^2=11.061*	0.004*
CH	0 (0%)	0 (0%)	6 (50%)	6 (75%)		
Vitamin D						
Median (minimum–maximum)	14.9 (14–15.9)	15.6 (5.2–25.7)	19 (5.7–27.8)	15.5 (8.5–27.4)	*H*=0.893	0.827
Mean±SD	14.9±1.3	15.4±8.1	17.9±8.9	16.9±6.17		

χ^2, χ^2 test; *H*, *H* for Kruskal–Wallis test; HAM-D, Hamilton Depression Rating scale; MDAS, Migraine Disability Assessment Scale. *P*, *P* value for association between MDAS and different parameter. *Statistically significant at *P* value less than or equal to 0.05.

studies reported that patients with migraine exhibit poor psychomotor speed, attention, and verbal memory performance compared with nonmigraineurs even during postictal periods [18].

Conversely, several longitudinal and cross-sectional studies have shown that migraine is not associated with cognitive dysfunction or decline and may even associate with better function or less decline [19,20]. Despite such inconsistent research findings on objective cognitive impairment, it is common that patients with migraine complain cognitive impairment in clinical practice. The perceptions of cognitive abilities are driven by comorbid symptoms rather than actual cognitive decline in patients with chronic pain. Therefore, cognitive problems in migraineurs is worthy to be approached from the assessment of complaints and its association with other comorbidities [18].

The current study was conducted to explore the association between vitamin D and migraine as a risk factor for depression and cognitive impairment among a sample of 30 Egyptian patients with migraine. Their demographic and headache-related clinical data including age, sex, duration of disease, frequency of attacks, presence or absence of aura and the type of migraine, and vitamin D level were completed.

Cognitive performance was assessed with MoCA scale for detecting cognitive impairment. Accordingly, the mean MoCA was 23.9±2.4 in the patient group

Table 5 Relation between Montreal Cognitive Assessment and different parameter (*N*=30)

	N	MoCA		Test of significance	*P*
		Mean± SD	Median (minimum–maximum)		
Type of migraine					
Migraine without aura	22	24.1±2.4	24 (21–28)	*t*=0.599	0.554
Migraine with aura	8	23.5±2.4	23 (21–27)		
Type of migraine					
Episodic	18	25.3±1.9	24 (23–28)	*t*=6.394*	<0.001*
CH	12	21.8±1.1	21.5 (21–24)		
MDAS					
No disability	2	28±0	28 (28–28)	*F*=10.639*	<0.001*
Mild	8	25.8±1.9	25.5 (24–28)		
Moderate	12	23.2±1.9	23.5 (21–26)		
Severe	8	22.3±1.2	22 (21–24)		
HAM-D					
Normal	10	26.2±1.9	27 (24–28)	*F*=8.525*	<0.001*
Mild	4	23.5±0.6	23.5 (23–24)		
Moderate	12	22.5±2	21.5 (21–26)		
Severe	4	23±1.2	23 (22–24)		

F, *F* for analysis of variance test; HAM-D, Hamilton Depression Rating scale; *t*, Student's *t* test; MDAS, Migraine Disability Assessment Scale; MoCA, Montreal Cognitive Assessment. *P*, *P* value for association between MoCA and different parameter. *Statistically significant at *P* value less than or equal to 0.05.

Table 6 Correlation between vitamin D and different parameter (*N*=30)

	Vitamin D	
	r_s	*P*
MoCA	0.016	0.933
Duration	–0.370	0.044*
Frequency	–0.546	0.002*

MoCA, Montreal Cognitive Assessment; r_s, Spearman coefficient. *Statistically significant at *P* value less than or equal to 0.05.

compared with 28.6±0.8 in the control group, and 73.3% of the patients have mild cognitive impairment, which is statistically highly significant. This result is in agreement with other studies [18,21,22]; however, some studies found that patients with migraine showed no cognitive impairment [23]. This difference may be owing to different inclusion and exclusion criteria, as it was a community-based survey.

Cognitive dysfunction was also found to be significantly related to severity of migraine. These findings suggest the existence of brain dysfunction during attacks of migraine, which can relate specifically to migraine or be a consequence of acute pain processing by the brain [24].

Cognitive dysfunction was also found to be significantly related to severity of comorbid depression. This is supported by the finding suggesting that people with chronic pain and depression may experience impairments in cognitive skills [25]. In the current study, cognitive impairment occurs in both migraine with aura and without, with no difference between both groups. This is in agreement with Tessitore *et al.* [26].

Cognitive impairment was also significantly related to chronic migraine than episodic form, and this is in agreement with Aurora and Brin [27].

In this study, the level of vitamin D was found to be significantly lower in patients with migraine than the control. This result is in agreement with other studies [28–30]. However, the result was not in agreement with Zandifar *et al.* [31], who found no relation between vitamin D and migraine. However, the result was from a small case report.

The current study also revealed a significant negative correlation between vitamin D, duration of disease, and frequency of attacks and that a larger number of monthly days with headache was related to vitamin D deficiency among migraineurs. Despite the limitation of small samples in the subgroup analysis, this association was consistently noted among patients with episodic and chronic migraine. This result is in agreement with Cho *et al.* [28] and also supported by the result of Thys-Jacobs [32], which reported dramatic reduction in frequency and duration of headaches after supplemental vitamin D administration.Studies have also shown no significant relationship between serum vitamin D

and migraine severity [28,33]. Our results are in line with these previous findings because the MDAS scores did not differ with vitamin D deficiency.

In the current study also vitamin D was not related to depression or cognitive impairment as associated comorbidities with migraine. It is not related to HAM-D or MoCA scales. This may be explained by the fact that these comorbidities occur due to main pathophysiology of migraine and associated central nervous system abnormalities.

In the current study, the effect of migraine on patient's daily life was assessed with MDAS. Accordingly, 6.7% of the total sample had no disability, 26.7% had mild disability, 40% had moderate disability, and 26.7% had severe disability.

Subjective pain is a common symptom in patients with depression, and in turn, chronic pain may trigger a depressive state [28,34,35]. In line with previous studies, our data also revealed significantly high levels of depression in patients with migraine.

The current study also revealed that migraine severity was significantly related to severity of depression and this is in line with Lee *et al*. [18] and Lantéri-Minet *et al*. [18,36].

Conclusion

Cognitive impairment and depression seem relatively common in migraine, which is not related to vitamin D deficiency but to migraine and its severity. This may be owing to the main pathophysiology of migraine and associated central nervous system abnormalities. This also indicates that vitamin D deficiency is not just an effect of the progression of migraine but truly an aggravating cofactor. Therefore, vitamin D may be used as an adjuvant treatment for decreasing migraine severity and associated comorbidities.

Recommendation

We recommend to perform this study on a larger population and to perform clinical trials with vitamin D to assess its effect on migraine severity and its associated comorbidities.

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Conflicts of interest

There are no conflicts of interest.

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