

Vitamin D Deficiency and Its Correlates in Migraine Patients

Sir,

Serum vitamin D levels have been associated with migraine. Seasonal variation of serum vitamin D levels depicting higher levels in summer and lower levels in autumn-winter were matched with that of migraine attacks.^[1] A lower level of serum vitamin D was associated with migraine.^[2] Despite a probable relationship between migraine and serum vitamin D, clinical correlates associated with vitamin D deficiency were not clearly identified in migraine patients. Therefore, we identified vitamin D deficiency and its correlates in migraine patients for suggesting the role of vitamin D supplementation in migraine therapy.

We conducted a prospective, cross-sectional study. We invited new patients with migraine who visited our headache clinic. The Institutional Review Board of Kyungpook National University Hospital approved the study (approval number KNUH 2016-03-009). All participants gave written informed consent. We collected their clinical characteristics and conducted the Migraine Disability Assessment Scale,^[3] the Patient Health Questionnaire-9,^[4] the Generalized Anxiety Disorder-7,^[5] the Insomnia Severity Index,^[6] and the Fatigue Severity Scale.^[7] All eligible patients measured serum vitamin D levels by radioimmunoassay. Vitamin D deficiency is defined as a serum 25 (OH) D of less than 20 ng/ml.^[8] By this value, we divided patients into two groups as having vitamin D deficiency and having no deficiency. We identified factors associated with vitamin D deficiency by using univariate and multivariate analyses.

Initially, 380 new patients were visited our clinic. Of them, 92 patients were excluded due to concurrent vitamin D intake ($n = 57$), probable migraine ($n = 18$), refusal to the study ($n = 15$), younger age ($n = 1$), and older age ($n = 1$). Finally, 288 patients were eligible for the study. Their mean vitamin D level is 15.8 ± 5.7 ng/ml (range: 3.4-34.9 ng/ml). Of them, 240 patients (83.3%) had vitamin D deficiency. According to the existence of vitamin D deficiency, characteristics of patients are manifested in Table 1. Factors associated with vitamin D deficiency by univariate analyses are denoted in Table 2. Younger age, chronic migraine (CM), anxiety, and fatigue were associated with vitamin D deficiency. However, BMI, the amount of sunlight exposure, the date of blood sampling, headache intensity, and disability were not associated with it. Factors associated with vitamin D deficiency by multivariate analyses are listed in Table 3. CM (adjusted Odds Ratio [AOR] 4.038, 95% confidence interval [CI] 1.890-8.628, $P < 0.001$) and younger age (AOR 1.031, 95% CI 1.006-1.058, $P = 0.017$) were selected.

We found major correlates for vitamin D deficiency were CM and younger age. The role of vitamin D deficiency on migraine chronicity has not been clearly identified. The

Table 1: Characteristics of migraine patients by serum vitamin D levels

	Mean±SD (range) or number (%)	
	25 (OH) D ≥20 ng/ml (n=48)	25 (OH) D <20 ng/ml (n=240)
Age (years)	42.9±12.0 (20-64)	39.0±13.5 (20-68)
Gender, female	41 (85.4)	194 (80.8)
Education (years)	13.2±2.9 (6-18)	13.0±3.1 (3-20)
BMI	22.0±2.7 (16-30)	22.5±3.4 (15-36)
Sunlight exposure (/week)		
Less than 1 hour	20 (41.7)	98 (40.8)
1 hour to less than 8 hours	22 (45.8)	112 (46.7)
8 hours or more	6 (12.5)	30 (12.5)
Date of blood sampling		
October-March	19 (39.6)	125 (52.1)
April-September	29 (60.4)	115 (47.9)
Type of migraine		
Migraine with aura	3 (6.3)	27 (11.3)
Migraine without aura	45 (93.7)	213 (88.7)
Migraine chronicity		
EM	38 (79.2)	125 (52.1)
CM	10 (20.8)	115 (47.9)
MOH	3 (6.3)	24 (10.0)
Age at onset (years)	31.4±12.6 (13-58)	28.3±11.7 (6-60)
Duration of migraine (years)	11.5±8.6 (0.3-31)	10.7±9.1 (0.5-42)
Associated symptom		
Nausea/vomiting	39 (81.3)	204 (85.0)
Photophobia	24 (50.0)	122 (50.8)
Phonophobia	31 (64.6)	150 (62.5)
Osmophobia	20 (41.7)	118 (49.2)
VAS	7.7±2.4 (0-10)	7.5±2.3 (0-10)
MIDAS (days)	19.6±18.0 (0-70)	25.8±30.4 (0-181)
Depression, > 7 on PHQ-9	11 (22.9)	82 (34.2)
Anxiety, > 5 on GAD-7	9 (18.8)	89 (37.1)
Insomnia, >15 on ISI	5 (10.4)	43 (17.9)
Fatigue, >3.21 on FSS	21 (43.8)	146 (60.8)

25 (OH) D=25-hydroxyvitamin D; BMI=Body Mass Index; EM=episodic migraine; CM=chronic migraine; MOH=medication overuse headache; VAS=Visual Analog Scale; MIDAS=Migraine Disability Assessment Scale; PHQ-9=Patient Health Questionnaire-9; GAD-7=Generalized Anxiety Disorder-7; ISI=Insomnia Severity Index; FSS=Fatigue Severity Scale

pathogenic mechanism of migraine chronicity presumes to be associated with a neurotransmitter imbalance and upregulation of inflammatory pathways in CNS resulting in central amplification of peripheral pain signals.^[9] Vitamin D has anti-inflammatory effects in the body by reducing the release of pro-inflammatory cytokines and suppressing T-cell responses.^[10] So vitamin D deficiency may promote inflammatory pain mechanisms associated with CM. Another

Table 2: Factors associated with serum vitamin D deficiency by univariate analyses

Variable	β	SE (β)	OR (95% CI)	P
Age	0.023	0.012	1.123 (0.998-1.048)	0.042
Gender	0.328	0.441	1.389 (0.586-3.294)	0.456
Education	0.028	0.053	1.029 (0.927-1.142)	0.596
BMI	-0.053	0.051	0.948 (0.858-1.047)	0.295
Sunlight exposure, less than 1 hour				
Versus 1 hour to less than 8 hours	0.020	0.510	1.020 (0.375-2.773)	0.968
Versus 8 hours or more	-0.018	0.504	0.982 (0.365-2.639)	0.972
Date of blood sampling	0.506	0.322	1.659 (0.882-3.120)	0.116
Migraine type	0.643	0.630	1.901 (0.553-6.540)	0.308
CM	1.252	0.378	3.496 (1.666-7.336)	0.001
MOH	0.511	0.634	1.667 (0.481-5.774)	0.420
Age at onset	0.022	0.013	1.022 (0.996-1.049)	0.091
Duration of migraine	0.010	0.017	1.010 (0.976-1.044)	0.570
Nausea/vomiting	0.268	0.412	1.308 (0.584-2.930)	0.515
Photophobia	0.033	0.316	1.034 (0.556-1.922)	0.916
Phonophobia	-0.090	0.330	0.914 (0.479-1.745)	0.785
Osmophobia	0.303	0.320	1.354 (0.723-2.535)	0.343
VAS	0.038	0.072	1.039 (0.902-1.197)	0.595
MIDAS	-0.009	0.007	0.991 (0.978-1.004)	0.175
Depression	0.557	0.369	1.746 (0.846-3.601)	0.131
Anxiety	0.938	0.393	2.554 (1.182-5.520)	0.017
Insomnia	0.630	0.502	1.877 (0.702-5.017)	0.209
Fatigue	0.692	0.320	1.997 (1.067-3.736)	0.030

BMI=Body Mass Index; CM=chronic migraine; MOH=medication overuse headache; VAS=Visual Analog Scale; MIDAS=Migraine Disability Assessment Scale

Table 3: Factors associated with serum vitamin D deficiency by multivariate analyses

Variable	β	SE (β)	Adjusted OR (95% CI)	P
Constant	-3.807	0.683	0.022	<0.001
CM	1.396	0.387	4.038 (1.890-8.628)	<0.001
Age	0.031	0.013	1.031 (1.006-1.058)	0.017

CM=chronic migraine

possibility is, as vitamin D deficiency was associated with emotional distress and fatigue in our patients, these symptoms is likely to work as migraine triggers and induce repetitive migraine attacks. Under these pathogenic roles of vitamin D deficiency, we presume serum vitamin D levels may be an important correlate for migraine chronicity. The lower level of vitamin D in the younger age may be explained by disproportionately greater time spent indoors and less time spent outdoors among younger compared with older individuals.^[11]

Although we cannot conclude vitamin D deficiency is specific for migraine patients due to the lack of data for healthy controls, we presume migraine chronicity may accentuate vitamin D deficiency. As vitamin D supplementation is effective for decreasing frequency of migraine attacks in EM,^[12] further studies should be warranted to prove the therapeutic efficacy of vitamin D supplementation on CM. In addition, the relationship between serum vitamin D levels and therapeutic response should be also identified.

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Conflicts of interest

There are no conflicts of interest.

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