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The role of the vitamin D in neurology: interrelationships between headache, epilepsy and vitamin D deficiency

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F Mujgan Sonmez
Department of Child Neurology, Turgut Ozal University, Turkey

Correspondence: Prof. F. Mujgan Sonmez, Department of Child Neurology, Turgut Ozal University, Faculty of Medicine, Alparslan Turkes Street, No: 57, Bestepe, Ankara, Turkey, Tel +90-312-203-5250, Fax -5453, Email mjgsonmez@yahoo.com

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Abbreviations: DBP, vitamin D binding protein; VDR, vitamin D receptor; cAMP, cyclic AMP; PKA, protein kinase-A; PLC, phospholipase-C; MAP kinase, mitogen activated protein kinase; SPF, sun protection factor; NGF, nerve growth factor; GDNF, glial cell-derived neurotrophic factor; TTH, tension-type headache; HSE, high solar-exposure; LSE, low solar-exposure; no nitric oxide

Vitamin D (Calciferol) is a fat-soluble seco-steroid synthesized in the skin from 7-dehydrocholesterol (as hormone) or ingested with food (as vitamin). Ninety percent of Vitamin D is synthesized from the skin while a very small portion is absorbed from food. Vitamin D enters the circulation and is carried by vitamin D binding protein (DBP) to the liver where it is transformed into 25-OH-vitD in the liver and subsequently to 1,25-hydroxyvitamin-D (1,25-OH-vitD) in the kidney as a result of hydroxylation.[1–3]

The effect of vitamin D on tissues begins with the binding of its active form 1,25 OH vitD to vitamin D receptor (VDR).[4,5] VDRs are widely distributed in 38 different tissues including the brain where it is found in neurons, glial cells, brain macrophages, as well as the spinal cord and peripheral nervous system.[6,7]

Vitamin D is activated and degraded through the actions of cytochrome P450 hydroxylase enzymes.[8] While the synthesis to 1,25-dihydroxyvitamin D is catalyzed by α-1 hydroxylase (CYP27B1), C23/24 oxidation pathways that are catalyzed by CYP24A1 inactivates this active hormone. These hydroxylases are regulated by genomic and non-genomic mechanisms. 1,25-OH vitD induces genomic effects by regulating gene transcription via VDR and subsequent interaction of the VDR-1,25-D3 complex with its heterodimer partner retinoid-X-receptor and associated coactivators.[9,10] It also induces rapid non-genomic effects by activating various intracellular pathways cyclic AMP (cAMP), Protein kinase-A (PKA), Phospholipase-C (PLC), PI-3 kinase and mitogen activated protein kinase (MAP kinase) via the cell membrane.[10]

The large variations observed in the blood concentration of vitamin D worldwide may be due to common environmental factors such as latitude, seasonality, pollution, customs or cultural issues, diet, and fortified-food policies. In addition, individual sociocultural and behavioral factors such as clothing, use of sunscreens with high sun protection factor (SPF), sunbathing habits, skin pigmentation, time spent outdoors, and insufficient playgrounds may affect concentrations of vitamin D.[11,12]

It is accepted that lower normal level of 25-OH vitamin D level is about 30ng/dl. The World Health Organization defines vitamin D deficiency as a serum level of 25-OH vitamin D less than 20 ng/dl and insufficiency as a 25-OH vitamin D level less than 30ng/dl.[15]

Vitamin D deficiency is estimated to be present in more than 1 billion people worldwide.[16] A total of 9% of American children are vitamin D deficient and 61% have vitamin D insufficiency.[17] In Ankara, Turkey, in children 1-16years of age, the values for vitamin D deficiency and insufficiency were reported as 8% and 25.5%, respectively.[18]

In addition to behavioral and environmental predictors of vitamin D concentrations, genes may also play an important role. Heritability estimates of 25-hydroxyvitamin D range from 0.23 in Hispanics from the San Luis Vally in Colorado to 0.41 in Hispanics from San Antonio, Texas.[19]

Vitamin D and neurology

Vitamin D and its receptor have important regulatory effects during brain development, such as cell differentiation and apoptosis. It has been shown that vitamin D deficiency poses a risk for neurological diseases such as Alzheimer's and Parkinson's disease, multiple sclerosis, depression, schizophrenia, autism and epilepsy.[10]

Vitamin D and its receptors play important roles in the brain, such as regulation of cell growth and differentiation processes as well as neuroprotection. This effect of vitamin-D is related to neuronal calcium regulation, immune modulation, antioxidative mechanism, increased activity of nerve conduction and detoxification mechanisms. They also have mood-stabilizing effects.[24] Also, it was demonstrated in rats that vitamin D deficiency during the prenatal period led to dysregulation of the synthesis of approximately 30 different proteins in the developing brain and suggested that these deficiencies might be related to some neuropsychiatric diseases such as autism, depression and multiple sclerosis.[26–30]

In this section, we evaluate the association among vitamin D, epilepsy and headache.

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Epilepsy and vitamin D

In the literature, several studies have suggested an association between low vitamin D and seizures[31,32] Some animal studies also support an anticonvulsant effect of vitamin D.[33–35] In our study, we evaluated the levels of vitamin D after the diagnosis of epilepsy and in the initial period before starting drug therapy. We also evaluated patients according to those presenting during longer versus shorter daylight periods and compared results with the control group. We found that in all of the groups, vitamin D levels were lower than in the control group.[36]

Several hypotheses suggested to explain the role of the vitamin D deficiency in the pathogenesis of epilepsy;

a. Vitamin D may positively modulate brain neuromediators and receptors via GABA-A receptors.

b. Via the effect on calcium metabolism: Calcitriol may lead to increased plasma and decreased brain calcium concentrations, thus reducing neuronal hyperexcitability and seizures.[34]

c. The vitamin D/VDR endosome system: Vitamin D may affect seizures by acting via VDR to induce certain genes in the brain encoding cytokines and the enzymes of neurotransmitter metabolism.

Vitamin D downregulates interleukin 6 and upregulates anticonvulsant growth factors such as glial cell-derived neurotrophic factor and neurotrophin-3.[4] The localization of VDR to the plasma membrane caveolae results in the activation of signal transduction pathways. The interaction of the ligand-bound VDR with signal transduction pathways (PKC or MAP-kinase) stimulates exocytosis or opening of chloride or calcium channels.[37]

Headache and vitamin D

A relationship has been posited between vitamin D levels and chronic pain such as extremity, neck and joint pains in clinical randomized controlled studies.[38] The number of studies that support a role of vitamin D deficiency in headache is low.[38–46] Thys-Jacobs et al.,[39,10] reported that there was a statistically significant decrease in migraine attacks after treatment with vitamin D and calcium in two patients with premenstrual syndrome and two patients with postmenopause.

Vitamin D deficiency and insufficiency was reported as 14.8% and 25.9%, in adult patients with chronic migraine.[42] Krusz et.al.,[43] investigated the vitamin D levels in a study including 100 patients with headache as well as patients with chronic pain without headache and found no statistically significant difference between the two groups. In children with migraine, the prevalence of recurrent headache in patients with vitamin D deficiency was found statistically significantly higher in comparison with the normal population.[44]

It was reported that vitamin D levels in patients with headache were lower in comparison with other two groups including chronic musculoskleletal pain and chronic fatigue and that headache prevalence was increased with decreasing vitamin D levels.[45] Cayır et.al.,[46] reported that vitamin D intake decreases stroke frequency in children diagnosed with migraine who are treated with both vitamin D and amitriptilin.

In our study, we evaluated 147 patients with headache (migraine or other tension-type headache (TTH)) and 101 healthy controls, aged 5 to 16years. Each group was also divided into two separate sub-groups based on the presentation to the clinic in either high solar-exposure (HSE) and low solar-exposure (LSE). We retrospectively evaluated the levels of calcium, phosphorus, alkaline phosphatase, parathyroid hormone, and 25-OH vitamin-D3. Levels below 20ng/ml were described as vitamin D deficiency and levels of 20-30ng/ml as vitamin D insufficiency. The levels of 25-OH vitamin-D3 were statistically significantly lower when compared to the control group. This held true for both the HSE and LSE group compared to the control group.[47]

Several hypotheses have been put forth to explain how Vitamin D deficiency could cause headaches;[38] these include: decrease of nitric oxide (NO) production due to iNOS inhibition50, the regulatory effects of calcium channels due to downregulation of L-type Ca channels,[48,30] effect on the synthesis of serotonin 40 improvement of endothelial dysfunction,[49] the regulation of intracellular signal pathway activities and hypomagnezemia.[38]

According to the literature and to our studies, an evaluation of the association among Vitamin D, seizure and headache, suggest that vitamin D deficiency may play a role as a predisposing factor for headache and seizure in addition to various other underlying factors.

However, this conclusion needs to be supported with randomised clinical studies containing larger sample sizes and control groups. I think that further studies including more patients, together with the pathophysiological studies including evaluation of INOS, endothelial function and signal pathways, are necessarry to draw a firm conclusion regarding this issue.

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Conflicts of interest

Author declares there are no conflicts of interest.

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References

1. DeLuca HF. Overview of general physiologic features and functions of vitamin D1-4. *Am J Clin Nutr* . 2004;80(6 Suppl):1689S−1696S.
2. Kalueff AV, Tuohimaa P. Neurosteroid hormone vitamin D and its utility in clinical nutrition. *Curr Opin Clin Nutr Metab Care.* 2007;10(1): 12−19.
3. Holick MF. Vitamin D deficiency. *N Eng J Med* . 2007;357(3): 266−281.
4. Kalueff AV, Eremin KO, Tuohimaa P. Mechanisms of neuroprotective action of vitamin D3. *Biochemistry(Mosc).* 2004; 69(7):738−741.
5. Haussler MR, Jurutka PW, Mizwicki M, et al. Vitamin D receptor (VDR)-mediated actions of 1α,25(OH)$_2$vitamin D$_3$: genomic and non-genomic mechanisms. *Best Pract Res Clin Endocrinol Metab.* 2011;25(4):543−559.
6. Eyles DW, Smith S, Kinobe R, et al. Distribution of the vitamin D receptor and 1 alpha-hydroxylase in human brain. *J Chem Neuroanat* . 2005;29(1):21−30.
7. Janjoppi L, Katayama MH, Scorza FA, et al. Expression of vitamin D receptor mRNA in the hippocampal formation of rats submitted to a model of temporal lobe epilepsy induced by pilocarpine. *Brain Res Bull* . 2008;7480−7484.
8. Wjst M, Heimbecek I, KustschekeD, et al. Epigenetic regulation of vitamin D converting enzymes. *J Steroid Biochem Mol Biol* . 2010;121(1-2):80−83.

9. Omdahl JL, Morris HA, May BK. Hydroxylase enzymes of the vitamin D pathway: expression, function, and regulation. *Annu Rev Nutr.* 2002;22:139−166.
10. Fernandes de Abreu DA, Eyles D, Feron F. Vitamin D, a neuro-immunomodulator: implications for neurodegenerative and autoimmune disease. *Psychoneuroendocrinology.* 2009;34(Suppl 1):265−277.
11. Holick MF. Vitamin D: a D-Lightful health perspective. *Nutr Rev.* 2008;66(10 Suppl 2):S182−S194.
12. Karohl C, Su S, Kumari M, et al. Heritability and seasonal variability of vitamin D concentrations in male twins, *Am J Clin Nutr.* 2010;92:1393−1398.
13. Schoor MN, Lips P. Worldwide vitamin D status. *Best Pract Res Clin Endocrinol Metab*. 2011;25(4):671−680.
14. Bischoff-Ferrari HA, Govannucci E, Willett WC, et al. Estimation of optimal serum concentrationsof 25-hidroxyvitamin D for multiple health outcomes. *Am J Clin Nutr.* 2006; 84(1):18−28.
15. Prevention and management of osteoporosis. *World Health Organ Tech Rep Ser* . 2003;921: 1−164.
16. Bell DS. Protean manifestations of vitamin D deficiency, Part 1: The epidemic of deficiency. *South Med J* . 2011;104(5):331−334.
17. Gordon CM, DePeter KC, Feldman HA,et al. Prevalence of vitamin D deficiency among healthy adolescents. *Arch Pediatr Adolesc.* 2004;158(6):531−537.
18. Akman AO, Tumer L, Hasanoglu A, et al. Frequency of vitamin D insufficiency in healthy children between 1 and 16 years of age in Turkey. *Pediatr Int.* 2011;53(6):968−973.
19. Engelman CD, Meyers KJ, Ziegler JT, et al. Genome-wide association study of vitamin D concentrations in Hispanic Americans: the IRAS family study. *J Steroid Biochem Mol Biol*. 2010;122(4):186−192.
20. Luine VN, Sonnenberg J, Christakos S. Vitamin D: is the brain a target? *Steroids* . 1987;49(1–3):133−153.
21. Prufer K, Veenstra TD, Jirikowski GF, et al. Distribution of 1,25-dihydroxyvitamin D3 receptor immunoreactivity in the rat brain and spinal cord. *J Chem Neuroanat* . 1999;16(2):135−145.
22. Baas D, Prüfer K, Ittel ME, et al. Rat oligodendrocytes express the vitamin D(3) receptor and respond to 1,25- dihydroxyvitamin D(3). *Glia.* 2000;31(1): 59–68.
23. Hewison M. Vitamin D and the immun system: new perspectives on an old theme. *Endocrinol Metab Clin North Am*. 2010;39(2):365−379.
24. Harms LR, Burne TH, Eyles DW, et al. Vitamin D and the brain. *Best Pract Res Clin Endocrinol Metab* . 2011;25(4): 657−669.
25. Neveu I, Naveilhan P, Baudet C, et al. 1,25-dihydroxyvitamin D3 regulates NT-3, NT-4 but not BDNF mRNA in astrocytes. *Neuroreport* . 1994;6(1):124−126.
26. Oudshoorn C, Mattace–Raso FU, Van der Velde N, et al. Higher serum vitamin D3 levels are associated with better cognitive function. *Dement Geriatr Cogn Disord* . 2008;25(6):539−543.
27. Hoogendijk WJ, Lips P, Dik MG, et al. Depression is associated with decreased 25 hydroxyvitamin D and increased parathyroid hormone levels in older adults. *Arch Gen Psychiatry*. 2008;65(5):508−512.
28. Sutherland MK, Somerville MJ, Yoong LK, et al. Reduction of vitamin D hormone receptor mRNA levels in Alzheimer as compared to Huntington hippocampus: correlation with calbindin-28k mRNA levels. *Mol Brain Res*. 1992;13(3): 239−250.
29. Karampoor S, Zahednasab H, Ramagopalan S, et al. 25-hydroxyvitamin D levels are associated with multiple sclerosis in Iran: A cross-sectional study. *J Neuroimmunol* . 2016;290:47−48.
30. Brewer LD, Thibault V, Chen KC, et al. Vitamin D hormone confers neuroprotection in parallel with downregulation of L-type calcium channel expression in hippocampal neurons. *J Neurosci* . 2001;21(1): 98−108.
31. Christiansen C, Rodbro P, Sjo O. Anticonvulsant action of vitamin D in epileptic patients? A controlled pilot study. *Br Med J*. 1974;2(5913):258−259.
32. Holló A, Clemens Z, Kamondi A, et al. Correction of vitamin D deficiency improves seizure control in epilepsy: a pilot study. *Epilepsy Behav.* 2012;24(1):131−133.
33. Kalueff AV, Minasyan A, Tuohimaa P. Anticonvulsant effects of 1,25-dihydroxyvitamin D in chemically induced seizures in mice. *Brain Res Bull* . 2005;67(1−2):156−160.
34. Kalueff AV, Minasyan A, Keisala T, et al. Increased severity of chemically induced seizures in mice with partially deleted Vitamin D receptor gene. *Neurosci Lett* . 2006;394(1):69−73.
35. Siegel A, Malkowitz L, Moscowitz MJ, et al. Administration of 1,25-hydroxyvitamin D3 results in the elevation of hippocampal seizure threshold levels in rats. *Brain Res* . 1984;298(1):125−129.
36. Sonmez FM, Donmez A, Namuslu M, et al. Vitamin D deficiency in children with newly diagnosed idiopathic epilepsy. *J Child Neurol* . 2015;30(11):1428−1432.
37. Bell DS. Protean manifestations of vitamin D deficiency, part 3: association with cardiovascular disease and disorders of the central and peripheral nervous systems. *South Med J* . 2011;104(5):340−344.
38. Straube S, Andrew Moore R, Derry S, et al. Vitamin D and chronic pain. *J Pain.* 2009;141(1−2):10−13.
39. Thys-Jacobs S. Alleviation of migraines with therapeutic vitamin D and calcium. *Headache* . 1994;34(10):590−592.
40. Prakash S, Shah ND. Chronic tension-type headache vitamin D deficiency: *casual or causal association? Headache.* 2009;49(8):1214−1222.
41. Thys-Jacobs S. Vitamin D and calcium in menstrual migraine. *Headache*. 1994;34(9): 544−546.
42. Wheeler SD. Vitamin D deficiency in chronic migraine. In: 50nd Annual Scientific Meeting American Headache Society. Boston, MA, USA. 2008.
43. Krusz JC, Albright JP, Cagle J. Vitamin D Levels in Migraine and Headache Patients Compared to Patients with Pain Disorders. In: 52nd Annual Scientific Meeting American Headache Society, Los Angeles, USA. 2010.
44. O'Brien H, Hershey AD, Kabbouche MA, et al. Prevalence of vitamin D deficiency among pediatric patients with recurrent headaches. In: 52nd Annual Scientific Meeting American Headache Society, Los Angeles, USA. 2010.
45. Knutsen KV, Brekke M, Gjelstad S, et al. Vitamin D status in patients with musculoskeletal pain, fatigue and headache: a cross-sectional descriptive study in a multi-ethnic general practice in Norway. *Scand J Prim Health Care*. 2010;28(3):166−171.
46. Cayir A, Turan MI, Tan H. Effect of vitamin D therapy in addition to amitriptyline on migraine attacks in pediatric patients. *Braz J Med Biol Res* . 2014;47(4):349−354.
47. Sonmez FM, Donmez A, Namuslu M, et al. OP30 - 2317: Vitamin D status in children with headache. A case control study. *Eur Paed Neurol* . 2015;19 (Suppl 1):S10.
48. Garcion E, Nataf S, Berod A, et al. 1,25- Dihydroxyvitamin D3 inhibits the expression of inducible nitric oxide synthase in rat central nervous system during experimental allergic encephalomyelitis. *Brain Res Mol Brain Res.* 1997;45(2):255−267.
49. Yiu YF, Chan YH, Yiu KH, et al. Vitamin D deficiency is associated with depletion of circulating endothelial progenitor cells and endothelial dysfunction in patients with type 2 diabetes. *J Clin Endocrinol Metab*. 2011;96(5):830−835.

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