The Role of the Vitamin D in Neurology: Interrelationships Between Headache, Epilepsy and Vitamin D Deficiency

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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].

Due to its 20 day half-life and easier measurable higher levels in circulating blood than that of the 1,25 form, 25-OH vitamin D is used to measure serum levels of vitamin D [13,14].

It is accepted that lower normal level of 25-OH vitamin D level is about 30 ng/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 30 ng/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 1-16 years 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].

In autoradiographic studies conducted in the brains of vertebrates, it was shown that 1,25(OH)2D3 is found in the forebrain, hindbrain, spinal cord and sympathetic ganglion [6,20].

In autoradiographic and immunohistochemical studies, it was shown that VDR is present in pituitary cells [21-23]. VDR was expressed in temporal, orbital and singulate cortex, talamus, stria terminalis, amidala, olfactory system, CA1, CA2, CA3, CA4 pramidal neurons in hypophysis of the adult brain [21].

The synthesis of nerve growth factor (NGF) is regulated by 1,25(OH)2D3 [24]. 1,25(OH)2D3 upregulates NGF, neurotrophin 3 (NT3) and glial cell-derived neurotrophic factor (GDNF) and downregulates neurotrophin 4 (NT4) [25]. It was shown at

the molecular levels that rats with vitamin D deficiency have persistantly low NGF levels.

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.

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 musculoskeletal 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 16 years. 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 20 ng/ml were described as vitamin D deficiency and levels of 20-30 ng/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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