Original article

Vitamin D status in children with headache: A case-control study

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SUMMARY

Background: Vitamin D is a fat soluble vitamin with hormonal properties, plays crucial functions in bone and mineral metabolism and has important regulatory functions in brain development, cell differentiation and apoptosis. Some studies have shown a link between vitamin D deficiency and headache.

Material and methods: In this study, 147 patients with headache (migraine or either tension-type headache (TTH)) and 69 healthy controls, aged 5 to 16 years, were evaluated. Each group was also divided into two separate sub-groups based on 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 2030 ng/ml as vitamin D insufficiency.

Results: The levels of 25-OH vitamin-D3 were statistically significantly lower when compared to the control group (17.1 ± 9.4 vs. 25.8 ± 12.8 ng/mL respectively; p < 0.001). This held true for both the HSE and LSE group compared to the control group (for the group 1; 24.6 ± 11.8 vs. 32.1 ± 10.6 ng/mL respectively; p = 0.007, and for the group 2; 14.9 ± 6.8 vs. 19.6 ± 13.5 ng/mL respectively; p = 0.003). Also in headache subgroups (migraine and TTH), vitamin D levels were significantly lower than the control group (17.3 ± 9.0, 16.9 ± 9.9 and 25.8 ± 12.8 ng/mL respectively; p < 0.001).

Conclusion: There may be a relationship between vitamin D deficiency and headache, with particular significance in LSE. We suggest that this conclusion needs to be supported with randomised clinical studies containing a larger numbers of samples and controls.

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1. Introduction

Headache is frequently seen at child neurology clinics. Migraine pathophysiology is not clear, but common hypotheses are neurovascular theory and neurogenic inflammation [1], pain occurs due to an increase in the neurotransmitters nitric oxide (NO) and vaso-intestinal peptide (VIP) [1,2].

Vitamin D is a hormone which is synthesized 90% in the epidermis by ultraviolet B light (UVB) aid [3]. It is transformed into 25-OH-vitD in the liver subsequently to 1,25-hydroxyvitamin-D (1,25-OH-vitD) in the kidney [3]. The effect of vitamin D begins with the binding of 1,25-OH vitD to vitamin D receptor (VDR), 1,25-OH vitD induces genomic effects via VDR and non-genomic effects by activating various intracellular pathways (cyclic AMP, Protein kinase-A, Phospholipase-C, PI-3kinase and MAP kinase) [4]. VDRs are found in the brain; in particular, in neurons, glial cells, brain macrophages, spinal cord and peripheral nervous system [5]. Vitamin D deficiency increases risk of neurological diseases such as Alzheimer, multiple sclerosis, epilepsy, depression, schizophrenia and autism [4].

Low levels of vitamin D may cause chronic musculoskeletal pain [6]. There are very few studies examined the relationship between vitamin D deficiency and headache [7–16]. Only two of them were reported in pediatric populations [12,16].

The hypotheses that explaining how Vitamin D deficiency causes headaches are [6]: a) the enzyme iNOS is involved in the synthesis of NO which regulates cell migration, the immune response, and apoptosis. Activation of 1α-hydroxylase increases the level of calcitriol, which inhibits iNOS expression and reduces NO production. Deficiency causes inflammation via increased iNOS [6,17] b) regulatory effects of calcium channels; Vitamin D may lead to...
increased plasma and reduced brain Ca concentrations, by stimulating or inhibiting the expression of several Ca-binding proteins, so, deficiency may cause neuronal hyperexcitability [18]. c) Dysregulation of serotonin metabolism; Vitamin D, via tyrosine hydroxylase, has an effect on the synthesis of serotonin. So, deficiency causes depression (important for migraine and tension type headache (TTD)) [6]. d) Genetic factors; the presence of VDRs in the hypothalamus which is a region for migraine pain sensation [8] can support the hypothesis of vitamin D contribution in migraine. Taql and Fokl gene polymorphisms are associated with migraine without aura [19]. e) The improvement endothelial dysfunction; matrix metalloproteinases (MMPs) are proteolytic enzymes that are responsible for remodeling the extracellular matrix. Calcitriol inhibits MMP-9 in humans [20]. f) Vitamin D inhibits some intracellular signal pathway activities. Deficiency causes inflammation in conditions involving extravascular inflammatory pain like migraine [4] and (g) hypomagnesemia. Vitamin D deficiency causes hypomagnesemia and chronic pain (important for TTD) [8].

The objective of this study is to examine the relationship between subclinical vitamin D deficiency and headache in patients between 5 and 16 years of age with headache (this age range encompasses school-age children in Turkey).

2. Materials and methods

2.1. Participants

The records of 400 patients between the ages of 5 and 16 who presented with complaints of headache to the department of Child Neurology at Turgut Ozal University Faculty of Medicine between November 2011 and June 2013 have been retrospectively evaluated. Patients with symptoms and signs of chronic diseases (e.g., metabolic, skin, liver, gastrointestinal, bone or renal disease, mental retardation, cerebral palsy), diseases that cause malabsorption and immobilization, a history of dietary restrictions, or family history of osteoporosis, and those using any medications that might affect bone metabolism (nonsteroidal anti-inflammatory drugs, calcium, vitamin D, or steroids), and those with incomplete laboratory parameters were excluded from the study. A total of 150 children were included in the study according to these criteria. Three children (2%) were determined to have migraine and epilepsy and were excluded from the study.

The remaining 147 patients (84 female, 63 male) were grouped as either migraine or TTH according to the criteria in the ‘International Classification of Headache Disorders’-III (ICHD-3 beta version) set out by the International Headache Association [21]. All evaluations and classifications were made by a single child neurologist. Gender, age, family history, physical and neurological examination findings, EEG, neuroimaging and laboratory tests including calcium (Ca), phosphorous (P), alkaline phosphatase (ALP), parathyroid hormone (PTH), and 25-OH vit D levels were recorded. Due to the high prevalence of vitamin D deficiency in our area [22], Vitamin D and bone markers were evaluated as a part of routine laboratory tests in our child neurology and pediatric outpatient clinic from the year 2010 onward. The control group included 69 healthy children (29 female, 40 male) without headache who were admitted to the pediatric outpatient clinic for checkup before undertaking athletic or school activities. Gender, age, physical and neurological examination findings and same laboratory parameters were also recorded in the control group.

The patient and control groups were separated into two groups according to the intensity of sunlight and classified as either low solar exposure [LSE (October, November, December, January, February, March, April)] or high solar exposure [HSE (May, June, July, August, September)]. HSE was described as group 1, LSE was defined as group 2. 25-OH vitD levels and other biochemical parameters were evaluated in the total headache group, as well as the migraine and TTH sub-groups. Subsequently, analyses were carried out among groups as well as seasonal comparisons with the control group.

2.2. Methods

The sera of all cases in the patient and control groups were evaluated at the Turgut Ozal University Faculty of Medicine Biochemistry and Hormone Laboratory. Serum Ca, P, and ALP levels were measured via spectrophotometric methods using the Roche Integra 800. Serum PTH levels were evaluated with a chemiluminescence immunoassay method using the Siemens Centaur XP. Serum 25-OH vitamin D levels were studied via High Performance Liquid Chromatography (HPLC) method using by the Shimadzu CTO-10ASVP (Shimadzu Corp., Kyoto, Japan). 25-OH vitD levels were categorized according to the classification set out by Holick et al. (2011), 25-OH vitamin D levels up to 20 ng/mL were accepted as “deficiency”, while values between 21 and 29 ng/mL were accepted as “insufficiency” and values of 30 ng/mL and above were considered as “normal” [23].

2.3. Statistical analysis

The data obtained from the patients and the control groups were transferred to the computer environment and the SPSS version 16.0 (SPSS Inc., Chicago, IL, USA) package software was used for statistical analysis. Kolmogorov Smirnov test was used to examine the conformity of the data to normal distribution. ‘Student t-test’ ‘Mann Whitney U’ tests and ANOVA test were used where appropriate to examine the continuous variables. Chi-square test was used to analyze categorical variables. The results were given as mean ± standard deviation or percentages. p < 0.05 level was accepted as statistically significant.

Ethical approval was obtained from the Hospital Ethics Committee of Turgut Ozal University, Faculty of Medicine (number: 698).

3. Results

Of the 147 patients that were evaluated; 68 (45%) were determined to have migraine, and 79 (53%) were determined as having TTH. The mean age of the patients was 11.28 ± 2.98 years, whereas it was 10.6 ± 2.5 years for the control group. There was no statistically significance between the total of headache group, migraine or TTH Group and the control in terms of gender and age (X² = 4.798, df = 2, p = 0.091) (Table 1).

The presentation at the clinic during the LSE period for the total headache group was statistically higher than the control group (X² = 248.487, df = 6, p < 0.001) and this held true for subtypes of headache groups (for migraine X² = 169.000, df = 3, p < 0.001; for TTH X² = 180.000, df = 3, p < 0.001). Also, 23% of the 147 patients had a positive family history of headache (Table 1).

Although there was no statistically significant difference in the Ca, P, ALP and PTH levels between the headache and the control group, the 25-OH vitD level was significantly lower in the patient group (p < 0.001) and this held true for both group 1 and group 2 as well (p = 0.007) and (p = 0.003), respectively (Table 2). The vitamin D level of the 147 patients in the LSE period was significantly lower than that of the HSE period (p = 0.001).

It was observed that the 25-OH vitD level was also significantly lower in the migraine and TTH groups in comparison with the control group (p = 0.001 and p < 0.001 respectively). The levels were also significantly lower for the patients with migraine in
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