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Short Communication

Vitamin D Deficiency and Associated Autism Phenotypes

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Abstract

A number of studies have assessed the effects of VD supplementation in children. Special interest, however, has been devoted to the effects that adequate blood concentrations of Vit D exert during periods of pregnancy and lactation that require an adequate vitamin D status to avoid disturbances that may affect not only the musculoskeletal system but also the central nervous system.

Development Vit D deficiency (DVD) is associated with alterations in the dopaminergic neurotransmitter systems. In contrast, recently published animal experiments indicate that adult vitamin D (AVD) deficiency is associated with more subtle neurochemical and behavioral phenotypes.

Gestational vitamin D deficiency has been associated with autism-related traits in a large population-based sample as well in other neurological alterations. Because gestational vitamin D deficiency is readily preventable with safe, and accessible supplements, these candidate risks factor warrants closer attention.

Keywords: *Vitamin D; Autism; Pregnant Women; Gestational Deficiency*

Introduction

Vitamin D (Vit D) plays an essential role in regulating calcium and phosphate metabolism and maintaining a healthy mineralized skeleton. Humans obtain Vit D from sunlight exposure, dietary foods and supplements.

In addition to its role in bone health, Vit D is of importance for many metabolic and physiological processes. Conversely, Vit D deficiency has been associated with unfavorable outcomes for human health, among which are autoimmune and allergic diseases such as type 1 diabetes, asthma, respiratory tract infections, chronic diseases such as several types of cancer, cardiovascular disorders but also many evidences have accumulated on the effects of supplementing children and pregnant women with Vit D.

Clinical and experimental data

A number of studies have assessed the effects of Vit D supplementation in children. In Italy, a study in children 2 - 15 years old with moderate Vit D deficiency showed that a 1500 IU dose of Vit D3/day for six months was appropriate to maintain normal to near-normal 25(OH)D levels [1]. Other studies have shown that Vit D3 supplementation of 400 IU/day, 1000 IU/day, 2000 IU/day, and 4000 IU/day in children ages 9 - 13 years was safe and effective in raising mean concentrations of 25(OH)D in a 12-week period [2,3].

Special interest, however, has been devoted to the effects that adequate blood concentrations of Vit D exert during periods of pregnancy and lactation that require an adequate Vit D status to avoid disturbances that may affect not only the musculoskeletal system but also the central nervous system.

Regarding this last point it should be noted how Vit D is easily transported from blood to milk (much less 25(OH)D); it is estimated that for every 1,000 IU of Vit D absorbed by the mother there are about 80 IU/liter of milk. These values allows us to understand what Vit D doses should be taken during lactation and how administering 25(OH)D is less suitable for the purpose instead. The lower binding strength to DBP makes Vit D more available and permeable in breast cells; however, 25(OH)D, despite being more bound to DBP, is also able to penetrate, albeit with less ease, into breast cells through the megalin-cubilin endocytotic system.

Otherwise 25(OH)D passes easily into the fetal compartment through the placenta, also bound to DBP, as it is transported by the endocytotic Megalin-Cubilin receptor system; trophoblasts express cytochrome CYP 27B1 and can transform 25(OH)D into the active metabolite Calcitriol, as well as exerting paracrine control over the metabolism of vit. D with the possibility of further hydroxylating 25(OH)D to 24,25(OH)2D in case of high production of 1α,25(OH)2D.

The fetal concentration of 25(OH)D is about 70% of the maternal concentration, while Vit D accounts for only 10%. It is appropriate to consider how during pregnancy Calcitriol concentrations tend to increase, to better meet the necessary demand for Ca, a need to which the activity of the enzyme CYP27B1 present in the fetal kidney, as well as in the placenta contributes, at least in part, to the related conversion of the 25(OH)D present. The increased presence of Calcitriol also plays a protective function on the development and protection of the placenta and fetus as well as playing a role in tolerance for embryo implantation.

Over the last decade a convergent body of evidence has emerged from animal experiments and clinical trials linking deficit in Vit D status with several adverse neuropsychiatric outcomes. Results show that the exposure to low Vit D content influences the nature of brain phenotypes, as well as exposures during gestation result in different phenotypes in comparison to adulthood condition. There is also robust evidence from animal experiments showing that transient developmental Vit D (DVD) deficiency is associated with changes in brain structure, neurochemistry, gene and protein expression and behavior.

In particular, DVD deficiency is associated with alterations in the dopaminergic neurotransmitter systems. In contrast, recently published animal experiments indicate that adult Vit D (AVD) deficiency is associated with more subtle neurochemical and behavioral phenotypes [4].

Vitamin D and autism

Recent epidemiological studies have provided evidence that lower concentrations of gestational 25-hydroxyvitamin D (25(OH)D) may be correlated with increased risk of Autism Spectrum Disorder (ASD) phenotypes.

In an Australian birth cohort, maternal mid-gestation 25(OH)D insufficiency was associated with increased offspring risk of high scores on the Attention Switching subscale of the Autism Spectrum Quotient and increased risk of language impairment. Offspring of mothers with low 25(OH)-Vit D concentrations (< 49 nmol/L - 20 ng/ml) were at increased risk for 'high' scores (≥ 2SD above mean) on the Attention Switching Subscale (odds ratio: 5.46, 95% confidence interval: 1.29, 23.05) [5].

The risk of women with Vit D insufficiency (≤ 46 nmol/L - 18 ng/ml) during pregnancy having a child with clinically significant language difficulties was increased almost twofold compared with women with vitamin D levels > 70 nmol/L - 28 ng/ml [6].

In a large study to estimate whether Vit D status was related to ASD 34 publications involving 20,580 participants were identified and the meta-analysis of 24 case-control studies demonstrated that children and adolescents with ASD had significantly lower Vit D concentration than that of the control group. Authors state that detection and appropriate intervention of Vit D deficiency in ASD patients and pregnant or lactating women have relevant clinical and public importance [7].

Recent models based on transient prenatal exposure to Vit D deficiency have found a range of persistent molecular (gene and protein expression), neurochemical and behavioural changes of interest to neuropsychiatry. Neonatal Vit D deficiency has been associated with an increased risk of schizophrenia and Autism Spectrum Disorder (ASD) [8].

The active form of Vit D (1,25 dihydoxyvitamin D) is known to impact on the function of voltage-gated calcium channels. Variants in genes coding for subunits of these same calcium channels (for example, CACNA1C) have been linked to risk of both schizophrenia and ASD [9].

In addition, low concentration of Vit D has been linked to other neurobiological features associated with autism. The neurobiological plausibility of the association between autistic spectrum disorder and schizophrenia is strengthened by several data indicating Vit D deficiency in early life affects neuronal differentiation, axonal connectivity and brain structure [10].

Calcitriol has been shown to influence the expression of tryptophan hydroxylase 2 (a key enzyme in the production of serotonin). Serotonin and Vit D have been proposed to play a role in autism. There are evidence that Vit D hormone (calcitriol) activates the transcription of the serotonin-synthesizing gene tryptophan hydroxylase 2 (TPH2) in the brain at a Vit D response element (VDRE) and represses the transcription of TPH1 in tissues outside the blood-brain barrier at a distinct VDRE.

The proposed mechanism explains 4 major characteristics associated with autism: the low concentrations of serotonin in the brain and its elevated concentrations in tissues outside the blood-brain barrier; the low concentrations of the Vit D hormone precursor 25-hydroxyvitamin D [25(OH)D3]; the high male prevalence of autism; and the presence of maternal antibodies against fetal brain tissue.

In a recent review of 20 experimental studies [11] it is reported that that improving Vit D status of children with ASD significantly reduced the severity of the general condition. Theoretically, Vit D can also affect neurodevelopment in children with ASD through its anti-inflammatory properties, stimulating the production of neurotrophins, decreasing the risk of seizures, and regulating glutathione and serotonin levels.

Finally, it is worth mentioning how both the Vit D receptor and the rate-limiting enzyme required for the production of 1,25 dihydroxyvitamin D, are expressed in neurons and glial cells in the brain [12].

Gestational Vit D deficiency has been associated with autism-related traits in a large population-based sample as well in other neurological alterations. Because gestational Vit D deficiency is readily preventable with safe, and accessible supplements, these candidate risks factor warrants closer attention.

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