



The Role of Vitamin D in the Pathophysiology of Schizophrenia

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Abstract

Background: The neurodevelopmental hypothesis of schizophrenia sets the importance of genetic and environmental factors, such as vitamin D deficiency, in an early critical phase of brain development, causing a disturbance that may affect the individual's health as a young adult when other events take place during the maturation of the brain.

Methods and Findings: Pubmed database was used to search the 57 articles included in this review. Individuals born in winter and early spring months, living at higher latitudes or in urban areas and migrating to colder climates, thus with less vitamin D levels, have increased risk of schizophrenia, while individuals with more uptake of vitamin D have lesser risk. Several epidemiologic studies have already shown an association between maternal vitamin D deficiency and increased risk of schizophrenia in the offspring. Animal developmental vitamin D deficient models suggest a possible dopaminergic dysfunction but there might be other mechanisms involved, such as a disruption in glutamatergic transmission. Therefore, adequate VD supplementation during critical phases of life, including pregnancy, may be relevant, since pregnant females are a risk group for vitamin D deficiency.

Conclusions: Epidemiologic studies and animal models suggest a role of low maternal levels of vitamin D in the pathophysiology of schizophrenia. More well-designed prospective studies are needed to strengthen the association, as well as clinical trials to evaluate the impact of vitamin D supplementation.

Keywords

Schizophrenia; Vitamin D; Vitamin D deficiency

Abbreviations

1,25(OH)₂D₃: 1,25-Dihydroxyvitamin D₃; 25(OH)D₃: 25-Hydroxyvitamin D₃; CNS: Central Nervous System; COMT: Catechol-O-Methyl-transferase; DA: Dopaminergic; DOPAC: Dihydroxyphenylacetic Acid; DVD: Developmental Vitamin D; E: Embryonic Day; GDNF: Glial Cell Line-Derived Neurotrophic Factor; HVA: Homovanillic Acid; LTP: Long-Term Potentiation; NGF:

Nerve Growth Factor; NMDA: N-Methyl-D-Aspartate; VD: Vitamin D; VDBP: Vitamin D Binding Protein; VDR: Vitamin D Receptor

Introduction

Schizophrenia is a chronic mental disease with a profound impact in the patient and families' lives, as well as great direct and indirect costs [1-3]. It usually begins during late adolescence and early adulthood. Its prevalence and incidence

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vary depending on the geographic location (>10-fold variation, increasing with latitude) and diagnostic criteria but the global estimated prevalence is about 1% with an average incidence rate of 15.2 per 100,000 [2-4].

Concerning pathophysiology, the classic dopamine hypothesis is based on the increased dopamine levels in the brain during the psychotic episodes, which explain the efficacy of antidopaminergic drugs in treatment [3]. Recently, a new hypothesis has been conceived: the neurodevelopmental hypothesis. This theory sets the importance of genetic and environmental factors in an early critical phase of brain development (prenatal, perinatal and first years of life), causing a disturbance that may be silent at first but then it may affect drastically the individual's health as a young adult when other events take place during the maturation of the brain [5].

Studies estimate that schizophrenia has about 80% of heritability [1-3]. However, this is probably an underestimation of the environmental contribution [4]. Many environmental factors increase the risk of schizophrenia: prenatal exposures like advanced paternal age, infections, gestational diabetes, preeclampsia and malnutrition; perinatal exposures, such as prolonged labour and hypoxia, low birth weight, prematurity, winter-spring birth; and postnatal exposures, like urban environment growth, living as an ethnic minority following emigration and drug abuse [1,3-5].

Several maternal micronutrients have been related to an increased risk of schizophrenia, such as elevated homocysteine and iron, essential fatty acids, retinoids and vitamin D (VD) deficiency [6]. Actually, there is strong evidence that prenatal VD deficiency can produce profound alterations in adult brain. It has been associated to a range of neuropsychiatric diseases, such as multiple sclerosis, depression, Parkinson disease, autism and schizophrenia [5-7]. A "critical window" during pre and perinatal periods has been proposed, when low VD levels "imprints" on several tissues, in addition to genetic factors and adults exposures, leading to an increased risk of certain diseases later [8].

This paper will review the VD metabolism, the VD deficiency and schizophrenia relation (epidemiology and proposed pathophysiological mechanisms) and if there is any benefit of VD supplementation in disease prevention.

Methods

Pubmed database was used to search the articles for this review with the following query: ("vitamin d" OR "25-hydroxyvitamin D3" OR "25-hydroxyvitamin D2" OR "25(OH)D3" OR "25(OH)D2") AND "schizophrenia". On November 2016, 170 articles were found. Based on the paper's title and abstract reading, 61 articles, written in English or Portuguese, covered these review subtopics (physiology of VD, VD deficiency as a risk factor for schizophrenia, its effects on brain development and adult brain function and VD supplementation for prevention). Following full-text reading, 54 articles were included. Three additional articles were included to elucidate the neurodevelopmental hypothesis of schizophrenia. Therefore, 57 articles were used in this review.

Results and Discussion

■ Physiology of Vitamin D

In humans, VD can be obtained from diet (VD₂/3) but mainly through the epidermal exposure to UVB radiation with wavelengths of 290–315nm (VD₃, which lasts 2-3 times more in circulation than the one ingested) [9-11]. Furthermore, 100% of the VD₃ obtained from skin binds the VD binding protein (VDBP), as opposed to only 60% from diet or supplementation [11]. It undergoes two hydroxylation reactions, forming 25-hydroxyvitamin D₃ (25(OH)D₃) and 1,25-dihydroxyvitamin D₃ (1,25(OH)₂D₃ or calcitriol), the active form [9,10]. Since 25(OH)D₃ is the main circulating form, it is the best biomarker to assess VD status [12,13].

During pregnancy, maternal 25(OH)D and 1,25(OH)₂D cross the placenta after 4 weeks of gestation, with 25(OH)D being more easily diffused and reaching 87% of the mother's levels. However, as placenta expresses 1 α -hydroxylase, it is able to produce the calcitriol [14-16]. The fetus is completely dependent on VD maternal stores. In fact, studies have shown a positive correlation between maternal and fetus 25(OH)D₃ levels [17]. Mother and fetus 1,25(OH)₂D total levels and VDBP increase since the first trimester but the free form increases only at the third trimester [14-16].

The brain is able to produce calcitriol as it expresses 25-hydroxylase and 1 α -hydroxylase [10]. Actually, 1,25(OH)₂D₃ synthesis was shown in activated microglial cells *in vitro*

[8]. 24-hydroxylase gene, coding the enzyme responsible for 25(OH)D₃ and 1,25(OH)₂D₃ degradation, is expressed on glial cells. Furthermore, an animal experiment showed that central nervous system (CNS) 1,25(OH)₂D₃ levels correlated with serum 25(OH)D₃ and not with serum 1,25(OH)₂D₃ levels, which suggests an *in situ* production of calcitriol in CNS [10]. So, CNS might be able to locally regulate the levels and availability of calcitriol [18]. The mechanisms through which 25(OH)D₃ or 1,25(OH)₂D₃ can cross the blood–brain barrier are still under discussion. Whether there are passive or energy-depending mechanisms involved is still unknown [10,17].

The biological effects of VD are mediated by its binding to vitamin D receptor (VDR), a nuclear receptor found in neurons and glial cells from several CNS regions such as cortex (temporal, frontal, parietal and cingulate), deep grey matter (thalamus, basal ganglia, hypothalamus, hippocampus, amygdala), cerebellum, brainstem nuclei, substantia *nigra* (dopaminergic neuron-rich area), spinal cord and ventricular system [9,19]. After ligand binding, VDR heterodimerizes with the retinoic X receptor and binds to specific areas in genetic promoters, regulating the expression of hundreds of genes involved in membrane transport, maintenance of nucleosome structure, signal transduction and brain morphology and function. Plus, there are effects mediated by VD binding to Membrane Associated, Rapid Response Steroid receptor that activates signal transduction pathways, such as calcium channels, that generate fast responses [9,19].

■ Vitamin D deficiency as a risk factor for schizophrenia

The latest update on neurodevelopmental theory of schizophrenia has suggested multiple risk factors, possibly with a cumulative and interactive effect, acting together on a genetic predisposed individual, at particular times of development, towards the clinical syndrome of schizophrenia. One of these risk factors is VD deficiency, particularly during gestation and infancy [20].

About 1 billion people worldwide has insufficient (21–29 ng/mL) or deficient (<20 ng/mL) VD levels, with pregnant females being a risk group given the increased nutritional needs and less outdoor activity, especially in the third trimester, particularly if occurring during winter [9,21]. Actually, VD deficiency is more prevalent among

women and minority populations [22]. An USA survey detected severe VD deficiency in 4% of white and 42% of black childbearing age women [23]. An UK longitudinal study that assessed 25(OH)D levels of pregnant and non-pregnant childbearing age Caucasian women showed that over 95% had insufficient levels [24].

Only about 1% of UVB is able to reach the surface of Earth. The longer the distance to travel, less photons reach it, which explains why living, in winter, on a location above and below 33° latitude makes VD production by sunlight exposure very reduced or even null [11]. A genomic study found that genetic variants related to schizophrenia and VD frequencies vary significantly with latitude [25]. Melanin acts like a natural sunscreen, thereby when exposed to similar conditions, white skin is able to produce more VD than dark skin [11,26]. Serum 25(OH)D has seasonal variation with maximal levels in late summer (August to October) and minimal levels in early spring (February to April) [14]. Data from a British birth cohort at the age of 45 years old showed that September was the month with the peak levels of 25(OH)D and February presented the nadir, also observed in a Danish cohort of postmenopausal women [11].

The hypothesis of prenatal VD deficiency being involved in the pathophysiology of schizophrenia states that individuals: (a) who were born in winter and early spring months; (b) living at higher latitudes in both hemispheres (such as Scandinavian countries); (c) living in urban areas (reduced sun exposure and outdoor activity); and (d) migrating to colder climates at an early age or the second generation migrants (especially those with darker skin) have increased risk of schizophrenia, and that (e) individuals with more uptake of VD have lesser risk [2,9,21].

Several epidemiologic studies have shown that maternal VD deficiency during the critical phases of gestation increases the risk of schizophrenia in the offspring [27]. Data from a little cohort study of dark-skinned mothers showed that women with lower 25(OH)D levels have greater rates of schizophrenia in their offspring [18]. A recent Danish cohort study based on neonatal dried blood spots showed that low levels of 25(OH)D in newborns were associated with twofold increased risk of developing schizophrenia later [18,28]. However, it also concluded that both decreased and increased levels of 25(OH)D can predispose to the disease [11,12,28]. The authors suggest the existence of

single-nucleotide polymorphisms that impair the conversion of 25(OH)D into calcitriol in a subgroup of individuals to explain this non-linear relationship, resulting in VD deficiency in individuals with high 25(OH)D₃ levels [19,28]. The population attributable risk for VD in this study was 43.6% [29]. Another study using third trimester maternal sera banked in Boston and Providence, USA, found no association between 25(OH)D levels and risk of schizophrenia, although there was a significant trend in a subgroup of black mothers. However, the sample was small and only one blood sample was used to estimate overall pregnancy VD status [30]. Recently, a Mendelian randomization approach, an efficient way to inquire the causality suggested by observational studies, concluded that serum 25(OH)D levels don't have a causal role in schizophrenia. However, this study focused on the effect of lifelong lower 25(OH)D levels, not considering the possibility of a specific critical exposure period, such as pregnancy, when low 25(OH)D increases schizophrenia risk [31]. A prospective population-based study couldn't find an association between maternal 25(OH)D and psychotic experiences in their 18 years-old offspring. It is an early age to evaluate schizophrenia development. Besides, the outcome was infrequent in the cohort, thus it lacked power to reject small to medium sized effects confidently [32].

■ Vitamin D deficiency effects on brain development and adult brain function

VD deficiency effects during the CNS development have been studied through animal studies, like VDR knockout, 1 α -hydroxylase knockout and developmental vitamin D (DVD) deficient models [9]. The best to understand the developmental neurobiology of schizophrenia is the latter, which produces a transitory VD deficiency in pregnant female rats and assesses the brain changes of their offspring. Female rats are submitted to a controlled environment of lightning and diet during six weeks before mating and through gestation in order to obtain deficient serum levels of VD. VD status returns to normal within 12h of the birth in the dams and after 14 days *postpartum* in the offspring. Calcium and phosphate levels don't change, however parathyroid hormone levels are elevated [17].

VD modulates proliferation, differentiation and apoptosis. Experiments with neurosphere cultures showed that cultures from DVD-

deficient animal embryos had more neurospheres than controls [17,33]. When 1,25(OH)₂D₃ was administered, neurosphere formation was inhibited, but it had no effect on cultures from DVD-deficient embryos, suggesting that low 1,25(OH)₂D₃ during the critical periods of development produces persistent changes on progenitor cells [18]. DVD deficient rats have less differentiated brains with increased proliferation that leads to structural changes like increased global size and cerebral hemispheric length, cortical layer thinning and enlarged ventricle volume, when compared to controls [9,18].

In spite of its anti-proliferative role, a study showed that DVD deficiency in rats reduced the proliferation in the subgranular cell layer of the hippocampal dentate gyrus in adulthood and that haloperidol was capable of restoring it. The fact that this study focuses on the adult brain and not on the developing one, may explain this difference [34].

Evidence indicates an involvement of VD in neuronal differentiation, maturation and growing. *In vitro* experiments showed that 1,25(OH)₂D₃ stimulates the expression of several neurotrophic factors: nerve growth factor (NGF), involved in developmental neuronal growing and survival, especially cholinergic neurons projecting to the hippocampus and providing trophic support; glial cell line-derived neurotrophic factor (GDNF), which modulates dopaminergic (DA) neurons development, survival and function; and neurotrophin 3. It decreases the levels of neurotrophin 4 [9,17,18]. DVD deficiency neonates presented reduced levels of p75^{NTR}, involved on developmental apoptosis, and of NGF and GDNF [9,18].

VDR expression is firstly seen at embryonic day (E) 11.5 in the mouse brain and at E12 in the rat midbrain, coinciding with the birth of most dopamine neurons, and is widely distributed with a predominance in neuroepithelium and subventricular areas (an important site for neurogenesis) [9,35]. The VDR distribution throughout the CNS is very similar between humans and rats [18]. Concerning the gestation duration, the periods from conception to E18, E18 to postnatal day 11 and from that day on correspond to first, second and third trimester, respectively. Therefore, when the DVD deficiency is prolonged until weaning, there is a full coverage of the equivalent three human trimesters [36]. Studies found no

association between the most common VDR polymorphisms (*FokI*, *BsmI*, *ApaI* e *TaqI*) and schizophrenia in patients, so probably the effects seen in DVD deficient animals aren't caused by dysfunctional receptors, but by the transitory lack of ligand [37-39]. In fact, VDR knockout mice presented a completely different phenotype from DVD deficient models [38]. Also, a multigenerational study of a mutated VDR family found no association between VDR mutation and psychotic phenotypes [40].

It was demonstrated that DVD deficiency reduces the levels of early crucial factors for DA neuron specification, such as *Nurr1* and *p57Kip2*, and also of more mature markers, such as tyrosine hydroxylase, the rate-limiting enzyme of dopamine synthesis [41-44]. This strongly suggests that DA cells differentiation is delayed or decreased [33]. Also, it has been proven that DVD deficiency alters DA turnover, with diminished levels of catechol-O-methyltransferase (COMT), responsible to convert dopamine metabolite dihydroxyphenylacetic acid (DOPAC) to homovanillic acid (HVA), resulting in a low DOPAC/HVA ratio, although dopamine levels were normal. These findings point to a VD role in DA ontogeny [18,42].

DVD deficient rats offspring showed increased novelty-induced locomotion, which reflects a hyperactive subcortical DA system, correlating to the psychomotor agitation and disorganized behavior seen during positive symptoms [18,45]. It is unlikely to be caused by a stress-mediated mechanism since there is no alteration of hypothalamic pituitary adrenal axis-mediated stress responses [22]. Locomotion is increased after treatment with amphetamine [17]. Also, there is an enhanced locomotion after treatment with the psychomimetic MK-801, a N-methyl-D-Aspartate (NMDA) receptor antagonist, while the pretreatment with haloperidol significantly decreased the locomotor response to MK-801 in DVD deficient rats without significant changes in controls, which suggests there is a glutamatergic transmission disruption besides the DA anomalies [18,45]. VD deficiency during advanced gestation seems to be more relevant for this hiperlocomotive behavior since it is apparent when DVD deficiency begins in the late phase of pregnancy, while DVD deficiency restricted to the early phase doesn't cause it. Therefore, it seems to exist a critical period in which DVD deficiency causes a certain phenotypic outcome [17]. Also, DVD deficient rats have shown to have disrupted latent inhibition, which is a

measure of attentional processing impaired in schizophrenic, suggesting a disturbance in the ability to focus selectively on relevant stimuli [17,33].

Enlarged lateral ventricle volume only persists until adulthood if VD diet reintroduction is delayed until weaning [17]. This means that there is a postnatal window in which VD reintroduction may partially revert this phenotype [36]. Adult DVD deficient offspring also have decreased levels of NGF and some behavior alterations, including increased spontaneous locomotion in a novel environment and after NMDA antagonists, both selectively sensitive to antidopaminergic agents, and impaired attentional processing [46]. Also, adult DVD deficient female rats, contrary to the juvenile ones, have shown sensitivity to amphetamine-induced locomotion with increased DAT density or affinity in subcortical regions [45,47]. This resembles post-adolescent onset of positive symptoms in schizophrenics, which can be attenuated by antipsychotic drugs [33]. The DVD deficiency model doesn't replicate every feature of schizophrenia, however some of the changes are analogous, such as structural (enlarged ventricle volume, one of the most consistent neurobiological correlates of schizophrenia) and behavior anomalies (disrupted latent inhibition and sensitivity to NMDA antagonist and dopaminergic agonists) [9,18].

DVD deficient mice have a slightly different phenotype from rats. While DVD deficient rats had decreased head dipping, suggesting less exploratory behavior, DVD deficient mice showed significantly elevated rates on the hole board; however they both also showed novelty-induced hyperlocomotion, which may confound interpretation of head-dipping behavior [38,45]. Actually, most of the DVD models were conducted in genetically heterogeneous rats, with the fewer mice studies using genetically homogeneous inbred strains showing some contradictory results, indicating gene-environment interactions [45]. Besides developmental DA abnormalities, there are other disturbed mechanisms

DVD deficiency affects a range of proteins in the adult rat brain. Gene array and proteomics analysis of frontal cortex and hippocampus following DVD deficiency showed altered expression of 74 genes and 36 proteins, primarily from mitochondria, cytoskeleton and synapses, the majority down-regulated [45-48]. Another

study with rat nucleus accumbens found 33 altered proteins, namely calcium binding proteins, proteins involved in neurotransmission and mitochondrial functioning [49].

VD deficiency reduces the proline dehydrogenase gene expression (located on chromosome 22q11, a common deleted region that confers a genetic risk for schizophrenia), an enzyme that converts proline to glutamate. Given the proline role in neuro-modulating glutamatergic synapses in the hippocampus, it can contribute to glutamate abnormalities in schizophrenia. An adult population study found that over one third of the association between 25(OH)D insufficiency and schizophrenia may be explained by hyperprolinemia [50,51].

Phosphatidylinositol 3-kinase–protein kinase B pathway is involved in neurogenesis. It has been suggested that VD may activate this pathway, thus impaired signaling might be an explication for the structural changes observed with VD deficiency [52].

Another study assessed the hippocampal long-term potentiation (LTP), a cellular correlate of learning and memory. DVD deficient rats had increased LTP, reversed by haloperidol treatment. However, VD deficiency during adulthood had the contrary effect. The authors concluded that VD might regulate distinct neurophysiological targets during hippocampal development [17,53].

■ Vitamin D supplementation as a prophylactic approach of schizophrenia

Since the available schizophrenia treatments don't fully control the disease, prophylactic measures should be investigated, perhaps targeting possible risk factors, like increasing VD levels at critical times of development [20].

Solar exposure should be cautious since it can cause skin cancer. The ideal is to proceed to a sensible sun exposure, which means to never be exposed to such radiation capable of producing sunburn [11]. An alternative to produce VD from UV radiation is UV lamps. An UK study using low-intensity UV lamps at home daily for 15 minutes managed to raise serum 25(OH)D₃ levels from about 12 nmol/L to 32 nmol/L after a year, a substantial improvement [54]. Oily fish, eggs, vegetable oils, butter and liver are examples of food rich in VD [21]. Since daily food has few VD, even VD enriched food, it is difficult to obtain the amount needed from dietary source. Therefore, VD supplementation might be a

strong resource in populations with reduced sun exposure and low VD on their diet [11,15].

VD supplementation during gestational and perinatal periods seems to reduce the risk of developing schizophrenia later [9]. In fact, male children from a Finnish cohort who took 2000 IU of VD daily during their first year of life reduced their risk of developing schizophrenia in 77% compared with children that received less than 2000 IU daily [11,55]. However these results should be treated cautiously since the prevalence of lack of VD supplement was only 0.7% [55].

There are subgroups where VD supplementation may be particularly important, such as dark-skinned ethnic groups living in cold countries, childbearing age/pregnant women and women with schizophrenia (whose offspring have higher risk of developing the same illness) [23,28]. Evidence suggests that 25(OH)D levels during pregnancy should be 40–60ng/ml (100–150nmol), requiring a daily intake of 100µg (4000IU) of VD₃ [14,54]. The recommendations of VD daily intake to pregnant women from the Scientific Advisory Committee on Nutrition in the UK are 10µg (400IU), although still ineffective to solve VD insufficiency, as seen in an UK study [15,16,54]. Overall, there is still lack of consensus regarding the optimal dose [15,16].

The synthetic VD ligands with tissue-specific uptake development may be an interesting approach to avoid possible adverse effects, though VD intoxication is extremely rare and is often caused by ingestion of very high doses of VD (≥250 µg/d) during extended periods of time [11,16,56]. The clinical features include hypercalcemia, hyperphosphatemia and suppression of PTH that can lead to nephrocalcinosis and soft tissue calcification. Interestingly, no matter how much sun an individual is exposed to, VD intoxication doesn't happen because any excess in previtamin D₃ is photodegraded into products with no biological effect in the calcium metabolism [11].

Before any official recommendation, previous findings must be replicated and randomized controlled trials should be done although the relative low frequency of the disease and its late beginning make this a challenge. There are aspects that need to be clarified, such as VD deficiency prevalence, the possible nonlinear association with schizophrenia, the best timing to supplement, the neediest subgroups, adverse effects and costs [29].

Conclusion

Data from several countries of Europe, America, Asia and even Africa suggest that about 50% of the population worldwide is at risk of VD deficiency [11].

According to the neurodevelopmental hypothesis, prenatal exposure to VD deficiency interrupts the normal brain development predisposing the individual to long-term alterations, increasing the risk of schizophrenia. Several epidemiologic studies had already shown this association [27]. DVD deficiency behavior effects on adult animal offspring reflect a possible DA dysfunction but

there might be other mechanisms involved [18].

Despite improvements in schizophrenia management, the morbidity and mortality of the disease remain suboptimal, thus prophylactic measures should be investigated [9,57]. Adequate VD supplementation during critical phases of life, including pregnancy, may be relevant [12]. It might be a simple, safe and cost-effective intervention. However, more well-designed prospective studies are needed to strengthen the association between low VD and schizophrenia, as well as clinical trials to evaluate the impact of supplementation, establish recommendations and define target populations [17].

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