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REVIEW ARTICLE

Vitamin D deficiency as a risk factor for developing autism in childhood – literature review

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Abstract

Introduction and Objective. Both autism and vitamin D deficiency are increasingly prevalent among children. Vitamin D is believed to play a key role in many developmental pathways. The aim of this study is to review current knowledge of the relationship between autism spectrum disease and vitamin D deficiency among the paediatric population.

Review Methods. The review was performed using the PubMed and Cochrane database from the last 10 years. The terms 'autism' and 'vitamin D deficiency' were searched for. There were 15 articles in English on the PubMed database, 14 were included in the review. In the Cochrane database they were 16 position, 9 of which were included in the final analysis.

Brief description of the state of knowledge. Autism spectrum disorder (ASD) is a neurodevelopmental disorder. Typical signs are limited social relations, communication disorder and stereotyped and repetitive behaviours of varying severity. The etiology is still unknown, but nowadays the role of vitamin D deficiency isbeing investigated as a possible risk factor for ASD. There are many scientific reports of the mechanisms of action of vitamin D on the nervous system, as well as on the immune system and all cellular processes, which focus mainly on the regulation of calcium-depending systems, and antioxidant pathways. Vitamin D deficiency during pregnancy and early childhood can significantly affect the developing brain, predisposing to diseases such as autism and schizophrenia.

Summary. Further research is still needed to determine the real impact of vitamin D deficiency on the risk of neurodevelopmental disorders, as well as the possibility of using supplementation as a form of treatment.

Key words

children, autism, vitamin D deficiency

INTRODUCTION AND AIM

Autism (ASD – autism spectrum disorder) is a neurodevelopment disorder increasingly recognized in the paediatric population as one of the most common causes of disability in children under the age of five. A significant increase has been observed especially in the last 20 years which can be explained by improved diagnostics processes and greater awareness among parents. The disorder has been described by Leo Kanner, the Austro-American physician and psychiatrist, as a state of extreme loneliness that reflects the typical characteristics of ASD [1].

The development of the organism is very complex and requires the efficient functioning of many biochemical pathways. Calcium signalling plays a significant role in the whole process, from conception, through prenatal development, to the final development of the brain and nervous system, among other organs. It has been proven that vitamin D (VD) is involved in many processes necessary for the proper functioning of all these structures [2]. This is the reason why for many years is has been postulated that vitamin D deficiency leads to an increased risk of neurodevelopmental disorders, such as schizophrenia or autism [3]. Studies also show an association with multiple sclerosis (MS), Parkinson's disease, and Alzheimer's disease. [4].

This review of the literature aims to determine the real impact of disorder of the vitamin D-dependent pathways on the risk for developing autism spectrum disorders in the paediatric population.

MATERIALS AND METHOD

PubMed and Cochrane online bases were used to review the scientific literature on the subject. The main criteria for including a publication were that they dealt with the problem of the relationship between vitamin D deficiency and the development of autism. Key words used in the search were 'autism' and 'vitamin deficiency'. In order to analyze only the most recent results, the focus was on studies from the last 10 years. In the final analysis were included 14 articles from PubMed and 9 from the Cochrane database. The search procedure was in accordance with the Prisma standard, as shown in the Figure below.

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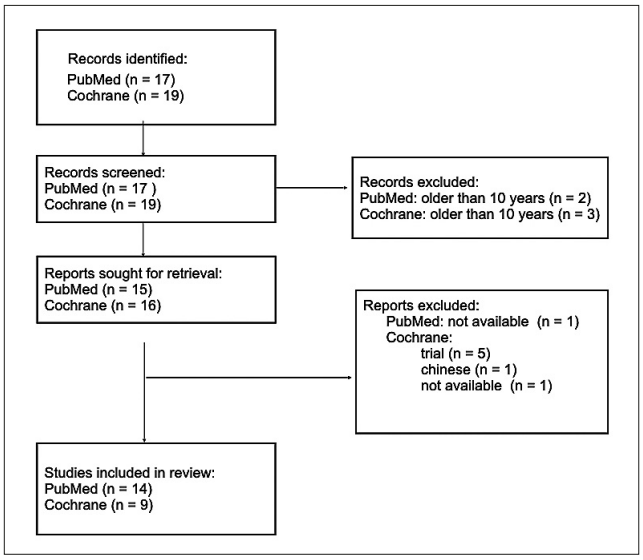

Figure 1. Search procedure

STATE OF THE KNOWLEDGE

The growing number of neurodevelopmental disorders worldwide prompts the search for potential risk factors, especially those that are modifiable. The etiology of autism spectrum disorders (ASD) is still not fully understood, but it is believed that the mutual influence of environmental and genetic factors play a fundamental role in the process. Studies have shown that a large number of genes are involved in the brain development of ASD patients, and the genetic background is clearly visible among families burdened with the disease. It is estimated that the heritability of ASD does not exceed 50%. It is also worth emphasizing that among monozygotic twins, the concordance is 50%, and among dizygotic twins about 20%; in many cases *de novo* mutations in special genes have also been described. [5]

The average age at which diagnosis is made in the USA is between the ages of 5 and 6 years, but it is believed that the number of undiagnosed cases by the age of 8 may be as high as 27%. (percentage of those diagnosed between 5–6) [6]. Autism spectrum disorders seem to be the leading cause of disability in children under the age of five. It is worth emphasizing that the link between vitamin D and ASD was first proposed by Dr. John Cannell in 2008. [1] The first symptoms of ASD are recognized typically in early childhood, at the age of 2 – 3 years, and persist throughout life [7]. Typical features, also included in the diagnostic criteria, are limited social relations, impaired communication, and stereotyped, repetitive behaviour [5,8]. Symptoms of varying severity persist throughout life. Patients often have additional disorders, most often olfactory, anxiety, and delays in motor development [7]. A relationship between the neurological symptoms and gastrointestinal problems associated with nutritional deficiencies, including (25(OH)D) deficiency, has been frequently frequently observed in ASD in the scientific literature. [22].

The pathogenesis of ASD has been linked many times to mutations in genes related to vitamin D, a vitamin belonging to the group of steroid hormones. It exists mainly in 2 forms: ergocalciferol (vitamin D2), which is synthesized by plants, and cholecalciferol (vitamin D3), which is synthesized in the skin under the influence of ultraviolet B (UVB) rays [9]. Vitamin D deficiency during the developing process of the brain can affect many signal pathways, such as neurotransmitter synthesis, differentiation of nerves cell, Ca2+-depending signalization, antioxidant activity, or mitochondrial activity. Both the vitamin D receptor and enzyme required to produce 1,25(OH)D are expressed in neurons and glial cells in the brain [10,16,17]. It is worth emphasizing that vitamin D- steroid hormon regulates about 3% of the genes in the coding genome [16].

In research by Javadfar (2020), people with ASD had lower serum vitamin D and higher serotonin and interleukin (IL)-6 levels than the control group [15]. Other peripheral markers of inflammation, e.g. IL-1β, IL-6 or TNF-α, have also been found to be elevated in children with ASD [20,22]. Vitamin D has pro-apoptotic and anti-proliferative properties and participates in neuronal differentiation [8,21], it also indirectly affects the expression of protein Nrf2 and the anti-aging protein Klotho, both of which are also important regulators of many cell signalling systems. These pathways increase cellular concentrations of antioxidants, which help maintain a normal reducing environment within the cell and results in preventing oxidative stress, while inhibiting the production of nitric oxide in other pathway and limiting the damage caused by reactive oxygen species in lipid membranes. Research by Berridge (2017) showed that vitamin D deficiency also affects changes in dopaminergic transmission. In many cases of ASD, mutations in genes involved in synaptic formation, such as SHANK and neuroligin, have been identified. SHANK proteins are present in neuronal connections. One of the consequences of the SHANK mutation is the reduction of parvalbumin expression in GABAergic inhibitory neurons, which is typical for autism. Studies have also shown that VD deficiency causes a decrease in the level of serotonin, which participates in the modeling of various stages of development of the nervous system. This is most evident in diseases such as attention deficit hyperactivity disorder (ADHD), autism, and schizophrenia.

Changes in Ca2+ dynamics during brain development may also cause a change in the balance between excitatory and inhibitory neurons. This can also be confirmation that ASD is associated with a high incidence of epilepsy. The same relation also applies to the decrease of GABA-ergic pathways [3,5]. Microglial cells may also be involved in these processes.

Vitamin D belongs to the family of steroid hormones, next to sex hormones, retinoids and cortisol. Most of our body organs have receptors for VD which plays a complex role, participating in calcium homeostasis and bone metabolism, regulation of the immune response, as well as hormonal, metabolic and neurodevelopmental processes. The influence of hypovitaminosis-D on the pathogenesis of asthma, cardiovascular diseases, diabetes, allergies or intestinal inflammation has been proved [11]. Scientific societies around the world have determined the recommended levels of vitamin D with optimal level of at least 30 ng/ml. Vitamin D deficiency is defined as serum 25(OH)D concentration < 20 ng/ml. The latest epidemiological data indicate that up to 30% of children and 60% of adults have an insufficient concentration of vitamin D in their serum. The reasons for this condition may differ: too low exposure to sunlight, low dietary vitamin D intake, obesity, liver or kidney failure, or certain groups of medications [9].

Enders et al. (2016) conducted a one-year cohort study that showed a deficiency of vitamin D in over 78% patients with ASD. In the control group, this deficiency was found in only about 57% [4]. Similar results were obtained by a team from the Department of Child Psychiatry in Tunisia, where research by Chtourou (2019), showed that over 60 % of autistic children had vitamin D deficiency [17]. During a one-year cohort study at a German Tertiary Care Hospital, almost 90% of the patients had vitamin D levels below reference [21]. Deficiency of this vitamin increases the risk of ASD more than 3 times [17]. Research by Ganta et al. (2022) showed that as a result of limiting time spent away from home due to the COVID-19 pandemic, the risk of vitamin D deficiency significantly increased. They described the cases of three boys with autism who, due to isolation and social restrictions, spent less time outdoors. The boys developed severe VD deficiency and symptoms of hypocalcaemia, life-threatening symptoms, and included low-energy fractures and convulsions. However, the boys responded well to treatment with calcium and vitamin D. These cases emphasize the need for thorough clinical observation of children with autism for hypovitaminosis D, because they are in the high-risk group. [12]

Research on the relationship between vitamin D deficiency during pregnancy and in early childhood and the risk of neurodevelopmental diseases have been conducted for years [13]. Although contradictory results have often appeared, the vast majority of literature emphasizes a significant relationship between autism and vitamin D-deficiency. Children of mothers with low levels of vitamin D during pregnancy were more likely to develop autism in their childhood [2]. Supplementation of vitamin D during pregnancy has been shown to reduce the risk of brain developmental disorders. Also, the degree of deficiency was positively correlated with the severity of the ASD.

First reports on the possibility of using vitamin D to treat autism originate from 2014 when vitamin D was administered intramuscularly and orally to a three-year-old boy with ASD. A significant improvement in his health was noticed after increasing the vitamin level [5,22]. Further research has shown that vitamin D supplementation may relieve ASD symptoms [15] in about 75% of autistic children. Vitamin D supplementation is considered as safe [16,23]. It has also been shown that vitamin D supplementation during pregnancy (5,000 IU/day) and during early childhood (1,000 IU/day) reduced the risk of autism in mothers who already had one child with ASD, from 20 % to almost 5% [16,18]. In a randomized controlled trial by Saad (2019), the autism symptoms of the children improved during a 4-month follow-up vitamin D3 supplementation, but not in the control group [18,19]. This confirms the role of vitamin D deficiency in the functioning of the nervous system of autistic patients. Many studies have also consistently shown that children conceived in winter have a 16% higher risk of being diagnosed with ASD, compared to children conceived in summer [1]. It is also worth emphasizing that the more frequent the occurrence of neurodevelopmental disorders in males may result from abnormal metabolism of steroid hormones, including vitamin D [11]. Also, in high-latitude countries, children of dark-skinned mothers are at particular risk of ASD with intellectual disabilities [14].

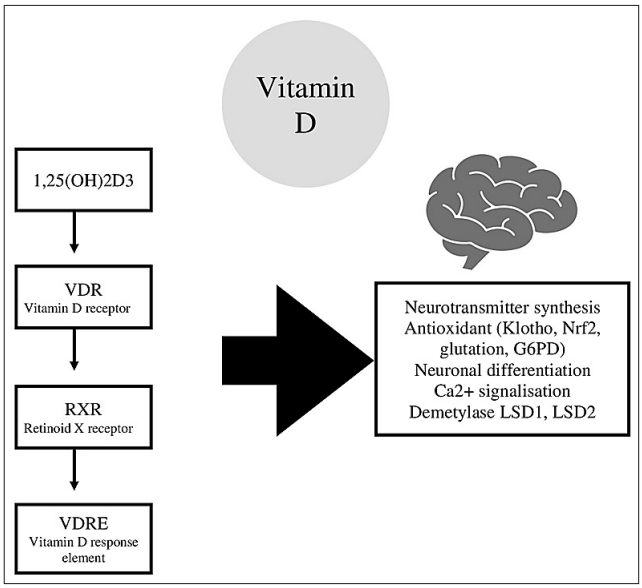

Figure 2. Vitamine D pathway

SUMMARY

The latest reports suggest a significant relationship between reduced levels of vitamin D and the occurrence of neurodevelopmental diseases, such as ASD. Taking into account that hypovitaminosis D in pregnant women and children at any age is easily treatable, further research on these relationships seems important. The results of previous studies are largely consistent in that vitamin D pathways play an important role in the development of autistic disorders among children.

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