eISSN (Online): 2598-0580

Bioscientia Medicina: Journal of Biomedicine & Translational Research

Journal Homepage: www.bioscmed.com

The Relationship between Vitamin D and Autism Spectrum Disorder

Budi Kristianto[1*], Nining Febriyana[1], Royke Tony Kalalo[1]

[1] Division of Child and Adolescent Psychiatry, Department of Psychiatry, Faculty of Medicine, Universitas Airlangga/Dr. Soetomo General Hospital, Surabaya, Indonesia

ARTICLE INFO

Keywords:
Vitamin D
Autism spectrum disorder
Genetics
Environment

***Corresponding author:**
Budi Kristianto

E-mail address:
drbudikristianto@gmail.com

All authors have reviewed and approved the final version of the manuscript.

https://doi.org/10.32539/bsm.v5i12.430

ABSTRACT

The tendency for autism spectrum disorders or also known as Autism Spectrum Disorder (ASD) is increasing globally, even becoming 1 per 54 in 2016. Until now, the cause of autism is not known for certain, ASD is considered to be a combination of genetic and environmental factors. One of the environmental factors in this case is related to nutrition, one of which is vitamin D. Vitamin D deficiency is often found among children with ASD. Several studies have shown that vitamin D is involved in various brain bioprocesses including neuromodulation and nerve transmission and brain function while also influencing inflammatory processes, autoimmune disorders, oxidative stress and also neurotransmitters that are widely associated with the possibility of ASD. This review aims to describe vitamin D deficiency may contribute to ASD disorders. Based on this, in the future, it is necessary to consider when treating patients with ASD to consider the need to check the patient's vitamin D levels and if there is a deficiency it can be advised to sunbathe and or be given additional vitamin D intake.

1. Introduction

The tendency of the occurrence of autism spectrum disorders or also called autism spectrum disorder (ASD) is increasing globally. Data from the Center for Disease Control and Prevention stated that the prevalence of ASD patients increased from 1 per 150 population in 2000 to 1 per 59 in 2014[1,2] and became 1 in 54 in 2016.[3] Until now, the exact cause of autism is not known, ASD is considered the cause as a combination of genetic and environmental factors.[4,5] ASD has a genetic component because more than 440 gene variants are found in about 30% of ASD patients.[6] Environmental factors in this case such as nutrition (folic acid, vitamin A and vitamin D), toxic (mercury), drugs, infections during pregnancy either due to viruses or bacteria, stress is thought to be one of the factors thought to play a role in the occurrence of ASD.[7]

Vitamin D is known to have an important role in brain homeostasis and neurodevelopment and plays an important role in gene regulation where vitamin D has been shown to bind to more than 2700 genes and regulate the expression of more than 200 genes. [8] One theory that links ASD and vitamin D is that proposed by Cannel, who says that during pregnancy and early childhood, vitamin D deficiency is the trigger for environmental factors for autism.[9]

Autism spectrum disorder

Autism spectrum disorder (ASD) is a developmental disorder characterized by impaired language and communication skills, social interaction and play and limited imagination with limited attention to interests and repetitive behaviors[10] and with its etiology not yet

fully understood with a high probability of being multifactorial.[11] Recent research on the etiology of ASD is the result of the interaction between genetic and environmental factors.[12] In DSM-5, autistic disorder is seen as a single entity and converted into a spectrum. The spectrum shows that the symptoms of this disorder vary from child to child.[10]

Factors that cause autism spectrum disorder

Until now, it is still not known with certainty the cause of ASD. There are various theories about the causes of autism, including biological theory where this theory is based on the fact that there is a close relationship with the incidence of mental retardation and an increased incidence of seizure disorders (25%) although until now it is not known exactly where the abnormality, suspected dysfunction of the brain stem, mesolimbic and even last associated with cerebellar involvement. There is also a link with immunology, in autistic children, it was found that there was a decrease related to the response of the immune system in some children, this became the basis for the possibility of immunological factors in some cases of autism with the discovery of antibodies in some mothers against the leukocyte antigens of their children with ASD brain cells, so that maternal antibodies can directly damage the neural tissue of the fetal brain, which is the cause of autism,[13] as well as linking viral infections based on the high frequency of autism disorders in children with congenital rubella infection, herpes simplex, encephalitis and cytomegalovirus so that experts suspect that viral infection is one of the causes of autism.[14]

Some research reported that autistic children have abnormalities in almost all brain structures, but the most consistent abnormalities are in the cerebellum or cerebellum which functions to control sublime functions and motor activities, as well as regulate attention and sensory circuits. If this circuit is damaged or disrupted it will interfere with the function of other parts of the central nervous system, such as the limbic system which regulates emotions and behavior. Autistic children also experience differences in some brain structures, especially in parts of the brain associated with executive function as well as communication and social skills such as the frontal cortex, temporal cortex, hippocampus and amygdala so that this causes children with autism to have difficulty in planning, less flexible thinking, difficulty in generalizing, difficulty in integrating complete information into something meaningful, and difficulty in being able to put oneself in the shoes of others.[15]

Disorders of the prefrontal cortex (frontal lobe) will lead to disruption of executive function, causing children with ASD to behave inappropriately and impulsively, lack of planning, fail to focus on what is happening.[16] Disorders of the occipital lobe will cause disturbances in spatial attention.[17] Disorders of the temporal lobe will cause disturbances in the ability to understand what is really going on.[16] Disorders that occur in the parietal lobe will cause an inability to coordinate what is seen with motor skills and cause impulsive tendencies.[18] Disorders that occur in the amygdala and hippocampus will cause disturbances in social, affective functions and difficulty storing new memories.[19] Damage that occurs in the basal ganglia can cause disturbances in cognitive function.[18] Damage to the cerebellum will make it difficult for children to divide attention and focus attention, but once focused it will be difficult to distract and unable to share attention with others.[18] Disorders of Broca's and Wernicke's areas will cause disturbances in language function, verbal expression and language comprehension skills.[20]

Vitamin D

Vitamin D is a fat-soluble vitamin and contains a steroid molecular structure that is needed in various metabolic processes in the body, consisting of two types, namely ergocalciferol (vitamin D2) usually found in plants and cholecalciferol (vitamin D3) found in animals.[21] The main source can be obtained from sunlight, intake from food sources and supplementation. The intensity of UVB rays from sunlight is low at 7 am in the morning, and increases in the following hours until 11 am. After 11 am, this intensity is relatively stable until 2 pm and then decreases until 4 pm. At 7 am, It's best to prevent vitamin D deficiency by being exposed to the sun for 15-30 minutes for 2-3 times/week.[22]

The main function of vitamin D is to help the formation and maintenance of bones along with vitamin A and vitamin C, parathyroid hormones and calcitonin, collagen protein and minerals calcium, phosphorus, magnesium and fluorine[21], in the body's defense against infectious diseases, allergies, malignancies and autoimmune diseases and is involved in natural and adaptive immunity[23]. Research on experimental animals vitamin D has a role in terms of brain proliferation, differentiation, neuroprotection, neurotransmission, neuroplasticity, increasing glutathione and increasing the regulation of genes involved in DNA repair, where these things are widely associated with the theory of ASD.[24]

The prevalence of the incidence of vitamin D deficiency that has been reported from various studies in the range of 14-42% in the general population. Research conducted on children aged 1 to 12.9 years found that 45% of children had vitamin D insufficiency.[22] Reference values for levels of 25-(OH) Vitamin D, deficiency less than 20 mg/dL, insufficiency 20-29 mg/dL and normal 30-100 mg/dL and toxic above 100 mg/dL.[25]

Relationship between vitamin D and ASD

As with all etiologically complex psychiatric conditions, ASD is believed to be an interaction between genetic and environmental factors that may negatively affect brain development.[26] A study in French found that vitamin D deficiency is involved in the breakdown of 36 proteins involved in mammalian brain development, including disrupting biological pathways for oxidative phosphorylation, redox balance, cytoskeleton maintenance, calcium homeostasis, chaperoning, post-translational modification, synaptic plasticity, and neurotransmission.[9]

Research using MRI shows that ASD children from birth to 12 months of age have abnormal abnormalities in brain volume compared to healthy children as controls.[27] This increase in brain volume is associated with increased gray matter, enlarged lateral ventricles and striatum. At the cellular level, brain enlargement in ASD involves an excess number of neurons in the prefrontal and dorsolateral cortex. This suggests altered cell proliferation and differentiation in autism. Research conducted on rats with vitamin D deficiency found neuroanatomical disturbances and proliferation of nerve cells. Vitamin D supplementation can increase antimitotic activity and reduce proliferation by inducing kinase inhibitors.[26] An evidence suggests that mitochondrial dysfunction and the presence of oxidative stress can predispose to ASD. Vitamin D may play a protective role at the mitochondrial level and its deficiency may contribute to mitochondrial dysfunction and oxidative stress in the brain of ASD individuals.[26]

There are two neurotransmitters that play an important role in synaptic communication in the brain, namely glutamate and gamma aminobutyric (GABA). Glutamate is metabolized by glutamic acid decarboxylase 65 (GAD 65) and glutamic acid decarboxylase 67 (GAD 67) to GABA. Many studies have reported a dysregulation of glutamatergic and GABAergic neurotransmission in the brains of autistic children. Higher levels of glutamate were found in the amygdala and hippocampus in ASD brains than controls. Post mortem studies show a 48-60% reduction in GAD 65 and GAD 67 in the brains of autistic patients compared to controls. Significant reductions in GAD 65 and 67 were also found in Purkinje cells and dentate cerebellar nuclei from brains of ASD patients.[26] Research in mice has shown that vitamin D can increase GABA synthesis in several brain tissues and upregulate GAD 65 and 67.[28]

The neurotransmitter that plays an important role in neurogenesis and neuronal differentiation during brain development is serotonin. Several studies have shown an abnormal serotonin system in the ASD brain. Studies using positron emission tomography have found low levels of serotonin transporters in the brains of autistic patients. Post-mortem ASD brain studies show lower density of serotonin receptors including 5-HT1A and 5-HT2A compared to controls.[29] In contrast to the brain, very high levels of serotonin are found in the blood compared to healthy people, where hyperserotonin is found in 30% of ASD patients.[26] Administration of vitamin D can induce tryptophan hydroxylase 2 (TPH2) in the brain as a serotonin synthesizer in the brain.[30]

There is a strong association between maternal infection and an increased incidence of ASD in

children. A number of postmortem studies have found that ASD brains have experienced inflammation characterized by activation of inflammatory cells in astrocytes and microglia in the brain.[26] Continuous inflammation will cause loss of connectivity and death of nerve cells.[31] Many studies of vitamin D have shown that vitamin D induces an anti-inflammatory response in several types of tissues, including the brain. Vitamin D can inhibit the synthesis of pro-inflammatory cytokines by targeting the activation of mitogen protein kinase phosphatase which is important in the regulation of immune responses,[32] suppresses the proliferation of activated B lymphocytes in autoimmune diseases so that a lack of vitamin D can have implications for the normal immune system.[26]

Meta-analysis research conducted by Liyao Song et al found that appropriate vitamin D supplementation was beneficial for symptom improvement in children with ASD, as demonstrated by SRS and CARS scores.[33] Oral vitamin D supplementation improves signs and symptoms of ASD.[34] In studies with children with ASD, it was found that children with a history of ASD had significantly lower vitamin D levels than healthy children and a significant association between autism severity and serum vitamin D levels.[35]

In a study conducted by Saad et al., on 122 children with ASD, 57% had deficiency D and 30% have vitamin D insufficiency.[34] Another study also found the same conclusion where vitamin D levels were lower in ASD children compared to controls.[36-38] Giving vitamin D3 supplementation (5000 IU/day) had a significant improvement in 80.72% of children with ASD, especially in the domains of irritability, social withdrawal, hyperactivity and stereotypic behavior.[39] Low serum vitamin D levels in children with ASD may be due to several factors, including inadequate intake, impaired vitamin D absorption, and possible geographic and lifestyle reasons associated with inadequate sun exposure.[40]

2. Conclusion

Autism spectrum disorder is a complex developmental disorder characterized by impaired communication, social interaction and the presence of repetitive behavior patterns. Vitamin D plays a role in inflammation, autoimmune disorders, oxidative stress and is also a neurotransmitter, although until now the exact mechanism is still being studied and explored regarding the mechanism of vitamin D deficiency and the occurrence of ASD. Vitamin D supplementation is inexpensive, easy to obtain and relatively safe and improve outcomes significantly in some children with ASD.

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