Core Symptoms of Autism Improved After Vitamin D Supplementation

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abstract

Autism spectrum disorder (ASD) is a common neurodevelopmental disorder caused by a complex interaction between genetic and environmental risk factors. Among the environmental factors, vitamin D_3 (cholecaliferol) seems to play a significant role in the etiology of ASD because this vitamin is important for brain development. Lower concentrations of vitamin D_3 may lead to increased brain size, altered brain shape, and enlarged ventricles, which have been observed in patients with ASD. Vitamin D_3 is converted into 25-hydroxyvitamin D_3 in the liver. Higher serum concentrations of this steroid may reduce the risk of autism. Importantly, children with ASD are at an increased risk of vitamin D deficiency, possibly due to environmental factors. It has also been suggested that vitamin D_3 deficiency may cause ASD symptoms. Here, we report on a 32-month-old boy with ASD and vitamin D_3 deficiency. His core symptoms of autism improved significantly after vitamin D_3 supplementation. This case suggests that vitamin D_3 may play an important role in the etiology of ASD, stressing the importance of clinical assessment of vitamin D_3 deficiency and the need for vitamin D_3 supplementation in case of deficiency.

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Autism, or autism spectrum disorder (ASD), is a neurodevelopmental disorder, characterized by impairment in social interaction and communication, accompanied by stereotyped and repetitive behavior, with varied levels of severity.[1–3] The genetic architecture of autism is complex, and its exact mechanisms remain elusive. Heritability estimates for ASD are about 50%.[4,5] Most likely the risk of autism arises from sporadic DNA mutations. Environmental factors, such as higher age of the father or obesity, may be related to these mutations.[6,7] Indeed, a growing body of literature suggests that certain modifiable risk factors such as maternal metabolic syndrome and certain vitamins such as vitamin D and folic acid either in utero or in early life may be associated with increased risk of autism[8].

Vitamin D deficiency may be one of the most important risk factors for several reasons. First, epidemiologic data on seasonal variation in birth rates and prevalence of autism suggest that maternal vitamin D deficiency is a risk factor for ASD[9,10]. Second, reduced serum vitamin D levels have been associated with alexithymia, a condition that shows high comorbidity with autism[11]. Third, there is reasonable theoretical support for a role of vitamin D in the etiology of ASD. Activated vitamin D upregulates the DNA repair gene, and vitamin deficiency during development may inhibit the repair of de novo DNA mutations during early fetal development. This would be in line with data from genetic studies showing an increased prevalence of rare mutations and copy number variation in autism[12]. In addition, vitamin D may reduce the severity of autism through its antiinflammatory actions, increasing T-regulatory cells and antiautoimmune effects and upregulating glutathione,

a scavenger of oxidative byproducts, thus contributing to a decreased risk of autism.[13]

Here we present a case with ASD and vitamin D_3 deficiency in whom supplementation of vitamin D_3 had a marked effect on the core symptoms of autism.

PATIENT PRESENTATION

The case is a 32-month-old male toddler who was referred to the Department of Pediatric Neurology and Rehabilitation of The First Hospital of Jilin University in Changchun, China, in 2014. Written informed consent was provided by the mother for permission to publish this case report. The patient was given the diagnosis of ASD according to the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*, diagnostic criteria[14] by a team of autism experts. His symptoms are summarized for each of the 3 domains of autism, as follows:

Social and communication impairment: no urge for social interaction, no response to facial expression or to other people, no social interactional smiling, not following instructions from his parents, no response when somebody calls his name, avoidance of eye contact and physical contact, strange gestures, unable to point to objects with his index finger, hugging other kids to express his affection, unable to play with peers properly, unable to share things with other kids

Qualitative deficits in language development and communication: delayed language development, occasionally says single words, regularly repeats some sounds and words

Restricted/stereotypic behavior and restricted interests: unable to play with toys properly, damages objects, tears papers repeatedly, smells surrounding objects (eg, table, chairs, etc), endless running and circling

In addition, this toddler suffered from temper tantrums. He was easily angered, attacked other children, and injured himself by banging his head against objects. He also had urine and fecal incontinence. Family history for psychiatric illness was negative. Brain computed tomography scan was normal, and karyotype analysis revealed no abnormalities (46XY). Screening of serum and urine metabolism revealed normal results. The patient's scores on autism assessments, including the Autism Behavior Checklist (score for normal children should be <53),[15] Childhood Autism Rating Scale (score for normal children should be <30),[15] and Severity of Illness of Clinical Global Impression (score for normal children should be 1),[16,17] were 80, 35, and 6, respectively. His serum 25-hydroxyvitamin D [25(OH)D] level was 12.5 ng/mL, as assessed by the high-performance liquid chromatography method. Serum vitamin D is considered adequate at $\geq$30 ng/mL and deficient at $\leq$10 ng/mL. Routine urine and serum calcium concentrations were not abnormal.

Vitamin D_3 has been intramuscularly administered at a dosage of 150 000 IU every month and orally administered at a dosage of 400 IU per day. Follow-up evaluation was performed at the end of the second month. The patient's parents reported a significant improvement in behavioral problems. Their child now begins to respond when his name is called. He is no longer preoccupied with running in circles and self-injury has almost stopped. He can now play with toys and actively asks his parents to hold him in their arms. He is no longer incontinent, and his abnormal smelling of objects is no longer present.

Laboratory tests revealed that serum 25(OH)D had increased to 81.2 ng/mL. Routine urine and serum calcium levels were not abnormal. Reevaluation scores for the Autism Behavior Checklist, Childhood Autism Rating Scale, and the Severity of Illness of Clinical Global Impression at the end of the follow-up period were 39, 28, and 4, respectively.

DISCUSSION

To our knowledge, this is the first case report of a case with ASD and vitamin D deficiency whose autism symptoms markedly improve after vitamin D supplementation. Vitamin D deficiency is a common nutritional disorder, and one of the most common undiagnosed medical conditions in the world. Recent studies suggested that vitamin D deficiency is a common phenomenon in children with ASD, and vitamin D deficiency may be involved in the process of autoantibody production in patients with autism.[18,19]

On the basis of the large body of evidence for a role of vitamin D in autism, symptoms of autism in this patient were assessed before and after vitamin D supplementation. The marked improvement in the relatively brief period of treatment that was observed in this case appears to be related to vitamin D supplementation. It seems unlikely that this improvement was caused by spontaneous natural development unrelated to serum vitamin D levels. Because no other medical abnormalities were found other than the vitamin D deficiency, it also appears unlikely that other diseases explain the improvements seen in this patient.

Vitamin D is regarded as a hormone that is active throughout our body, not only in regulating calcium and phosphate metabolism but also in its important role in brain development, in addition to its role in reducing the risk of chronic disorders such as multiple sclerosis, schizophrenia, tumors, cardiovascular disorders, and infectious diseases.[20,21] Calcitriol, the active form of vitamin D, is the metabolite created after 2-step hydroxylation of vitamin D from the diet or present in synthesized form in

the skin or in other organs such as the liver by 25-OH-hydroxylation or in the kidney by 1α-hydroxylation. However, over the past 2 decades, 1α-hydroxylase has also been found in organs other than the kidney, for example, in the pancreas, lungs, breasts, intestine, and brain. Therefore 25(OH)D can be hydroxylated to produce 1, 25-dihydroxyvitamin D in these organs by their autocrinal and paracrinal effects.[22,23]

In our case, vitamin D administration showed a treatment effect on the core symptoms of autism, although its mechanism remains unclear. Oxytocin and serotonin have been proven to be neuropeptides related to the behavioral manifestation in ASD, and vitamin D interacts with the metabolites of these 2 neuropeptides. In addition, vitamin D has been found to be involved in regulating immunologic dysfunction in autoimmune disease. Autoantibodies have also been found in children with ASD.[24,25] We postulated that vitamin D supplementation might play a role in the modulation of neuropeptides such as serotonin and oxytocin, regulating the dysfunctional immunologic process and repressing the production of autoantibodies in children with ASD.

In conclusion, this case report suggests that vitamin D may directly influence the core symptoms of autism. It is important to note that this single case observation cannot be generalized to all patients with ASD. It is hoped that this case report will encourage researchers to conduct further long-term controlled clinical trials with large sample sizes to investigate the possible role of vitamin D administration in treating ASD.

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