

Core Symptoms of Autism Improved After Vitamin D Supplementation

Feyiyoung Jia, PhD, MD^a, Bing Wang, MD^a, Ling Shan, MD^a, Zhida Xu, PhD^{a,b}, Wouter G. Staal, PhD^c, Lin Du, MD^a

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 D₃ (cholecalciferol) seems to play a significant role in the etiology of ASD because this vitamin is important for brain development. Lower concentrations of vitamin D₃ may lead to increased brain size, altered brain shape, and enlarged ventricles, which have been observed in patients with ASD. Vitamin D₃ is converted into 25-hydroxyvitamin D₃ 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 D₃ deficiency may cause ASD symptoms. Here, we report on a 32-month-old boy with ASD and vitamin D₃ deficiency. His core symptoms of autism improved significantly after vitamin D₃ supplementation. This case suggests that vitamin D₃ may play an important role in the etiology of ASD, stressing the importance of clinical assessment of vitamin D₃ deficiency and the need for vitamin D₃ supplementation in case of deficiency.

^aDepartment of Pediatric Neurology and Neurorehabilitation, The First Hospital of Jilin University, Changchun, China; ^bDepartment of Psychiatry, University Medical Center Utrecht, Utrecht, Netherlands; and ^cDonders Centre for Neuroscience, Radboud University Nijmegen Medical Centre, Karakter Centre for Child and Adolescent Psychiatry, Nijmegen, Netherlands

Dr Jia conceptualized and designed the study and drafted the initial manuscript; Drs Xu, Staal, and Du carried out the initial analyses and reviewed and revised the manuscript; Drs Wang and Shan collected the data for the case and critically reviewed the manuscript; and all authors approved the final manuscript as submitted.

The trial "Association of Polymorphisms of Vitamin D Metabolism-Related Genes With Autism and the Treatment of Autism with Vitamin D" has been registered at www.chictr.org/cn/proj/show.aspx?proj=6135 (identifier ChiCTR-CCC-13004498).

www.pediatrics.org/cgi/doi/10.1542/peds.2014-2121

DOI: 10.1542/peds.2014-2121

Accepted for publication Sep 24, 2014

Address correspondence to Lin Du, MD, Department of Pediatric Neurology and Neurorehabilitation, The First Hospital of Jilin University, Changchun, China, 130021. E-mail: zldulin@126.com

PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

Copyright © 2015 by the American Academy of Pediatrics

FINANCIAL DISCLOSURE: The authors have indicated they have no financial relationships relevant to this article to disclose.

FUNDING: No external funding.

POTENTIAL CONFLICT OF INTEREST: The authors have indicated they have no potential conflicts of interest to disclose.

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 autism⁸.

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 autism¹¹. 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 autism¹². 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 D₃ deficiency in whom supplementation of vitamin D₃ 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 criteria¹⁴ 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 ≥ 30 ng/mL and deficient at ≤ 10 ng/mL. Routine urine and serum calcium concentrations were not abnormal.

Vitamin D₃ 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 1 α -hydroxylation. However, over the past 2 decades, 1 α -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.

REFERENCES

1. Hollocks MJ, Jones CR, Pickles A, et al. The association between social cognition and executive functioning and symptoms

- of anxiety and depression in adolescents with autism spectrum disorders. *Autism Res.* 2014;7(2):216–228
2. Gialloreti LE, Benvenuto A, Benassi F, Curatolo P. Are caesarean sections, induced labor and oxytocin regulation linked to autism spectrum disorders? *Med Hypotheses.* 2014;82(6):713–718
3. Flashner BM, Russo ME, Boileau JE, Leong DW, Gallicano GI. Epigenetic factors and autism spectrum disorders. *Neuromolecular Med.* 2013;15(2):339–350
4. Sandin S, Lichtenstein P, Kuja-Halkola R, Larsson H, Hultman CM, Reichenberg A. The familial risk of autism. *JAMA.* 2014; 311(17):1770–1777
5. Gaugler T, Klei L, Sanders SJ, et al. Most genetic risk for autism resides with common variation. *Nat Genet.* 2014;46(8): 881–885
6. D'Onofrio BM, Rickert ME, Frans E, et al. Paternal age at childbearing and offspring psychiatric and academic morbidity. *JAMA Psychiatry.* 2014;71(4):432–438
7. Surén P, Gunnes N, Roth C, et al. Parental obesity and risk of autism spectrum disorder. *Pediatrics.* 2014;133(5). Available at: www.pediatrics.org/cgi/content/full/133/5/e1128
8. Cannell JJ. Autism and vitamin D. *Med Hypotheses.* 2008;70(4):750–759
9. Grant WB, Soles CM. Epidemiologic evidence supporting the role of maternal vitamin D deficiency as a risk factor for the development of infantile autism. *Dermatoendocrinol.* 2009;1(4):223–228
10. Grant WB, Cannell JJ. Autism prevalence in the United States with respect to solar UV-B doses: an ecological study. *Dermatoendocrinol.* 2013;5(1):159–164
11. Altbäcker A, Plózer E, Darnai G, et al. Alexithymia is associated with low level of vitamin D in young healthy adults. *Nutr Neurosci.* 2014;17(6):284–288
12. Cannell JJ, Grant WB. What is the role of vitamin D in autism? *Dermatoendocrinol.* 2013;5(1):199–204
13. Cannell JJ. Autism, will vitamin D treat core symptoms? *Med Hypotheses.* 2013; 81(2):195–198
14. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders.* 4th ed. Washington,

- DC: American Psychiatric Association; 1994
15. Rellini E, Tortolani D, Trillo S, Carbone S, Montecchi F. Childhood Autism Rating Scale (CARS) and Autism Behavior Checklist (ABC) correspondence and conflicts with DSM-IV criteria in diagnosis of autism. *J Autism Dev Disord.* 2004;34(6):703–708
16. National Institute of Mental Health. Rating scales and assessment instruments for use in pediatric psychopharmacology research. *Psychopharmacol Bull.* 1985;21(4): 714–1124
17. Endicott J, Spitzer RL, Fleiss JL, Cohen J. The global assessment scale: a procedure for measuring overall severity of psychiatric disturbance. *Arch Gen Psychiatry.* 1976;33(6):766–771
18. Duan XY, Jia FY, Jiang HY. Relationship between vitamin D and autism spectrum disorder [in Chinese]. *Zhongguo Dang Dai Er Ke Za Zhi.* 2013;15(8):698–702
19. Mazur-Kolecka B, Cohen IL, Gonzalez M, et al. Autoantibodies against neuronal progenitors in sera from children with autism. *Brain Dev.* 2014;36(4):322–329
20. Harandi AA, Shahbeigi S, Pakdaman H, Fereshtehnejad SM, Nikravesh E, Jalilzadeh R. Association of serum 25(OH) vitamin D3 concentration with severity of multiple sclerosis. *Iran J Neurol.* 2012;11(2):54–58
21. Hossein-nezhad A, Holick MF. Vitamin D for health: a global perspective. *Mayo Clin Proc.* 2013;88(7):720–755
22. Verstuyf A, Carmeliet G, Bouillon R, Mathieu C. Vitamin D: a pleiotropic hormone. *Kidney Int.* 2010;78(2):140–145
23. Gabriele S, Sacco R, Persico AM. Blood serotonin levels in autism spectrum disorder: a systematic review and meta-analysis. *Eur Neuropsychopharmacol.* 2014;24(6):919–929
24. Preti A, Melis M, Siddi S, Vellante M, Doneddu G, Fadda R. Oxytocin and autism: a systematic review of randomized controlled trials. *J Child Adolesc Psychopharmacol.* 2014;24(2):54–68
25. Patrick RP, Ames BN. Vitamin D hormone regulates serotonin synthesis. Part 1: relevance for autism. *FASEB J.* 2014; 28(6):2398–2413

Core Symptoms of Autism Improved After Vitamin D Supplementation
Feiyong Jia, Bing Wang, Ling Shan, Zhida Xu, Wouter G. Staal and Lin Du
Pediatrics 2015;135:e196; originally published online December 15, 2014;
DOI: 10.1542/peds.2014-2121

Updated Information & Services	including high resolution figures, can be found at: /content/135/1/e196.full.html
References	This article cites 23 articles, 1 of which can be accessed free at: /content/135/1/e196.full.html#ref-list-1
Post-Publication Peer Reviews (P³Rs)	One P ³ R has been posted to this article: /cgi/eletters/135/1/e196
Subspecialty Collections	This article, along with others on similar topics, appears in the following collection(s): Developmental/Behavioral Pediatrics /cgi/collection/development:behavioral_issues_sub Autism/ASD /cgi/collection/autism:asd_sub
Permissions & Licensing	Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at: /site/misc/Permissions.xhtml
Reprints	Information about ordering reprints can be found online: /site/misc/reprints.xhtml

PEDIATRICS is the official journal of the American Academy of Pediatrics. A monthly publication, it has been published continuously since 1948. PEDIATRICS is owned, published, and trademarked by the American Academy of Pediatrics, 141 Northwest Point Boulevard, Elk Grove Village, Illinois, 60007. Copyright © 2015 by the American Academy of Pediatrics. All rights reserved. Print ISSN: 0031-4005. Online ISSN: 1098-4275.

American Academy of Pediatrics

DEDICATED TO THE HEALTH OF ALL CHILDREN™



PEDIATRICS®

OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

Core Symptoms of Autism Improved After Vitamin D Supplementation

Feiyong Jia, Bing Wang, Ling Shan, Zhida Xu, Wouter G. Staal and Lin Du

Pediatrics 2015;135:e196; originally published online December 15, 2014;

DOI: 10.1542/peds.2014-2121

The online version of this article, along with updated information and services, is located on the World Wide Web at:

</content/135/1/e196.full.html>

PEDIATRICS is the official journal of the American Academy of Pediatrics. A monthly publication, it has been published continuously since 1948. PEDIATRICS is owned, published, and trademarked by the American Academy of Pediatrics, 141 Northwest Point Boulevard, Elk Grove Village, Illinois, 60007. Copyright © 2015 by the American Academy of Pediatrics. All rights reserved. Print ISSN: 0031-4005. Online ISSN: 1098-4275.

American Academy of Pediatrics

DEDICATED TO THE HEALTH OF ALL CHILDREN™

