

BY JOHN CANNELL, MD

AUTISM AND VITAMIN D

AUTISM and VITAMIN D

I (John Cannell, MD) recently learned that I have the **Broad Autism Phenotype**, or what some people call *mild autism*. Learning about this was like “coming out of the closet.” It explains so much of myself to me, especially my tendency to get obsessed with things. For the last 11 years, I have been obsessed with **vitamin D** and for the last four years, I have been obsessed with **vitamin D and autism**.

I first became interested in vitamin D when I learned it is not a vitamin. Instead, it is the only known substrate of a *secosteroid neurohormone* that functions, like all steroids, by turning genes “on” and “off”. That means it has as many different mechanisms of action as it does genes it regulates. Moreover, vitamin D regulates hundreds, if not thousands, of the 21,000 identified coding genes of the human genome.¹⁻³

Over the past few years, evidence has been mounting that vitamin D is involved in the autism epidemic.





In 2008, I first published⁴ and later extended⁵ epidemiological and animal data connecting vitamin D deficiency with autism. My second article is open access, discusses some of the autism/vitamin D evidence, and can be fully accessed at: www.lef.org/autism.

In 2009, *Life Extension® Magazine* published a detailed description of the theory.⁶

In 2009, Emily Deans, MD, wrote an extensive piece in *Psychology Today* outlining the theory of the connection between autism and vitamin D.⁷

In 2009, *Scientific American* asked, “What if vitamin D deficiency is a cause of autism?”⁸

In 2010, Kinney and colleagues at Harvard endorsed the vitamin D connection to autism.⁹

In 2012, Kočovská and colleagues, with senior author Professor Christopher Gillberg of the Gillberg Neuropsychiatric Institute in Sweden, reviewed the

evidence supporting the vitamin D connection to autism and called for “urgent research” into the connection.¹⁰

For the last year, I have been helping parents of autistic children correct their child’s vitamin D deficiency. My very preliminary and unscientific impressions are that if the child takes enough vitamin D (as long as they take enough cofactors with the vitamin D), about **25%** of the parents report *dramatic* improvements in their child’s autistic symptoms, about **50%** of parents report *significant* improvements, and **25%** of parents report no change.

How could vitamin D help autism, a condition that is highly genetic? Research has demonstrated that vitamin D has multiple mechanisms of action, many of which have been demonstrated to play a role in autism. Let’s take a look at four:

Anti-Inflammatory Actions

Some believe that autism is a disease of neuro-inflammation.^{11,12} According to scientific research vitamin D has profound anti-inflammatory actions.¹³ Experimental models show both direct and indirect anti-inflammatory effects of vitamin D involving both arms of the immune system (innate immunity and adaptive immunity).^{14,15}

Recent research reveals that activated vitamin D exhibits multiple anti-inflammatory effects.¹⁶ For example, vitamin D inhibits the synthesis and biological actions of pro-inflammatory prostaglandins, which are elevated in autism.¹⁶⁻¹⁸ Vitamin D also exerts anti-inflammatory activity through the inhibition of *nuclear factor-kappa B*, which is involved in abnormal signaling in autistic brains.^{19,20}

Could vitamin D help autistic children by reducing inflammation?

Autoimmune Actions

There are at least 80 recognized human autoimmune diseases with new diseases frequently added to the list.²¹ A number of autoantibodies to the brain have been identified in autistic children, causing some to believe that many cases of autism are autoimmune.^{22,23} Furthermore, the levels of such antibodies are directly associated with the severity of autism.^{24,25}

A recent study found that the level of one anti-neural autoantibody (anti-MAG) was elevated in **70%** of patients with autism.²⁶ The study found that higher

levels of anti-Mag were associated with significantly lower levels of vitamin D.²⁶ In the same study, low serum levels of *25-hydroxyvitamin D* were significantly associated with higher scores on an autism diagnostic assessment known as the **Childhood Autism Rating Scale**, indicating increasing severity of autism symptoms.²⁶

Could vitamin D help autistic children by reducing the blood levels of autoantibodies in autistic children?

Neurotrophins

Neurotrophins are the family of proteins that induce the development, function, and survival of nerve and brain cells. Vitamin D upregulates neurotrophins, such as NGF (nerve growth factor) and GDNF (glial-derived neurotrophic factor), up to five-fold.²⁷⁻²⁹

Could vitamin D help autistic children by increasing neurotrophins and thus help a damaged brain develop properly?

Antioxidants

Several research groups report that vitamin D upregulates the antioxidant glutathione in the brain.^{30,31} Glutathione is involved in the brain detoxification process because it participates in the scavenging of oxidative byproducts and the chelation (capture and excretion) of heavy metals.³¹⁻³³ Glutathione protects nerve cells and nerve conduction critical to mental processing, especially from toxins such as mercury.³³

Other research teams have reported that recent gene profiling has revealed several more antioxidants whose genes are directly upregulated by vitamin D.³⁴ This includes thioredoxin reductase 1 and superoxide dismutase, both of which function as antioxidants and detoxification agents.

Could vitamin D help autistic children by upregulating numerous antioxidants?

Theoretical Only

It's clear that various reasonable mechanisms exist for how vitamin D could help children with autism. Be it via anti-inflammatory actions, anti-autoimmune activities, upregulation of *neurotrophins*, or stimulation of antioxidant pathways, adequate doses of



vitamin D (enough to obtain natural blood levels of **50-80 ng/mL** of 25-hydroxyvitamin D) may be a potential treatment for some cases of autism.

However, such a claim is entirely theoretical. There are no randomized controlled trials, no open label trials, no case series, and not even one published case report of vitamin D helping autism.

Even though there are no studies proving the benefits of vitamin D in autism specifically, the proven safety and benefits of vitamin D, added together with the fact that vitamin D has been shown to have a beneficial effect on many of the mechanisms of action that underlie autism, make vitamin D a smart option for children with autism.

Parents who want to try it should thoroughly understand that no evidence, other than theoretical, exists for such an effect.

How To Start Your Child On Vitamin D

For parents who want to proceed on their own, the key to success is obtaining high physiological 25-hydroxyvitamin D blood levels around **80 ng/mL** (the same levels that are obtained by lifeguards in August).

As all studies show that autistic children are low in vitamin D, getting a *25-hydroxyvitamin D* blood test to start is usually unnecessary.

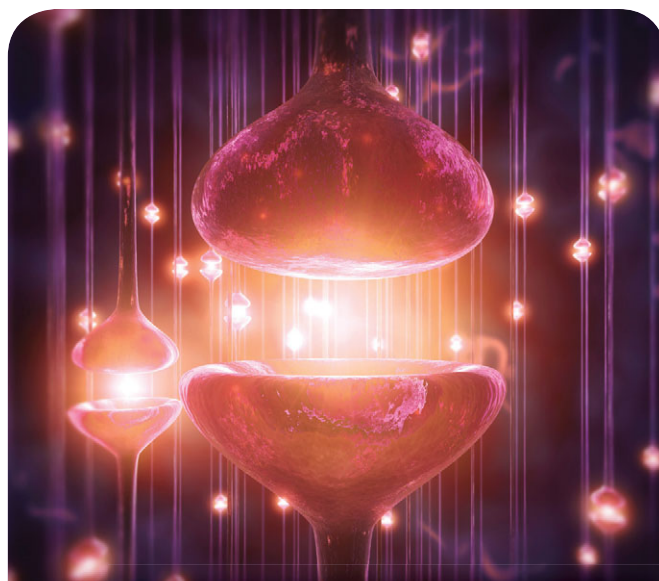
The first step is simply to give your child **50 IU** of vitamin D3 per pound of body weight per day. Liquid vitamin D is available from several sources.

So a 25-pound child would be started on **1,250 IU** each day of D3, a 50-pound child on **2,500 IU** each day, etc. This dose will usually result in mid-range physiological 25-hydroxyvitamin D levels (**40-60 ng/mL**), although some children may obtain higher physiological levels (**60-70 ng/mL**) on this dose.

The child should also be started on vitamin D's cofactors, such as vitamin K2 (**3 mcg** per pound of body weight) and nutrients in a multi-nutrient powder formula. If Life Extension Mix™ powder is used, ½ a scoop for every 25 pounds of body weight can be blended in juice or a smoothie. The roughly **700 IU** of vitamin D3 in one scoop of powder will help raise vitamin D levels.

After three months on the initial vitamin D dose, obtain another *25-hydroxyvitamin D* blood test. If the 25-hydroxyvitamin D level is by any chance over **80 ng/mL**, then the child's dose is adequate and nothing else needs to be done but to hopefully watch for improvements in core symptoms.

If 25-hydroxyvitamin D levels remain below **80 ng/mL**, then a proportional dose increase of **25 IU** vitamin D3 per pound of body weight is indicated.



What You Need to Know

Role Of Vitamin D In Autism

- Vitamin D inhibits the synthesis and biological actions of pro-inflammatory prostaglandins, which are elevated in autism.
- A number of autoantibodies to the brain have been identified in autistic children, causing some to believe that many cases of autism are autoimmune.
- Research has shown that high levels of certain brain-antibodies are associated with low vitamin D status.
- Vitamin D upregulates neurotrophins, the family of proteins that induce the development, function, and survival of nerve and brain cells, up to 5-fold.
- Vitamin D stimulates production of glutathione and several other antioxidant and detoxification enzymes.
- Even though there are no studies proving the benefits of vitamin D in autism specifically, the proven safety and benefits of vitamin D, added together with the fact that vitamin D has been shown to have a beneficial effect on many of the mechanisms of action that underlie autism, make vitamin D a smart option for children with autism.



For example, a 25-pound child on **1,250 IU** a day would increase to **1,875 IU** a day, and a 50 pound child on **2,500 IU** a day would increase to **3,750 IU** a day.

In three more months, obtain another 25-hydroxyvitamin D test and adjust doses accordingly. If 25-hydroxyvitamin D levels exceed **100 ng/mL**, simply reduce the dose by **10%** for every **10 ng/mL** the test is above **100 ng/mL**.

Levels above **100 ng/mL** do not mean “toxicity” as “toxicity” (asymptomatic hypercalcemia) is rare with 25-hydroxyvitamin D levels below **200 ng/mL**, and **200 ng/mL** is very difficult to obtain.³⁵ If these high doses make you nervous, have your child’s blood calcium level checked, and you will see your child’s calcium level is not high (**over 10.5 mg/dL**).

Keep adjusting the dose every three months based on vitamin D levels. It is important that you test for serum *25-hydroxyvitamin D* and not *1,25-dihydroxyvitamin D*. For children who do not tolerate venipuncture, an accurate blood spot test requiring only a finger prick is available at www.vitaminDcouncil.org.

For optimal absorption, give your child vitamin D during the meal of the day that contains the most fats. This may produce the optimal 25-hydroxyvitamin D levels suggested at the beginning of this section without having to resort to higher dosing.

As I said above, my very rough estimation is that around **75%** of autistic children seem to respond at least somewhat to higher doses of vitamin D after levels are around **80 ng/mL**.

Response Rates

To date, I have noticed that children who fall in one of the following categories tend to respond positively to vitamin D:

1. Children with reported seasonality of autistic symptoms (such as those with summer access to a swimming pool or similar extensive outdoor activities, in which the child is much better in late summer than he or she is in late winter) usually respond better.
2. Children who had a period of early normal development (as opposed to those who seem affected even as infants) seem to respond better.
3. Children with mild or moderate autism seem to respond better.
4. Children under the age of eight seem to respond better than older children do.

However, none of these, except perhaps a very distinct seasonality of symptoms, clearly predicts a response to vitamin D. In the same vein, some parents tell me that children with infantile onset of symptoms, children with more severe autism, or children older than eight have responded.

Unfortunately, my experience is that the **10-20%** of children with known genetic causes of autism (such

as Rett syndrome, fragile X syndrome, tuberous sclerosis, clear mitochondrial defects, submicroscopic deletions or duplications in DNA sequences, or deletions or duplications of chromosome regions) do not respond to vitamin D.

Parents who want me to participate in the diagnosis and treatment of their autistic child should contact my office in San Luis Obispo, California, for an appointment. There I will fully assess your child and give treatment recommendations to the parents. I will also be available for a limited number of tele-educational sessions via Skype, in which I will educate parents about vitamin D and its cofactors.

Summary

Over the past few years evidence has been mounting that vitamin D is involved in the autism epidemic. Research has demonstrated that vitamin D has multiple mechanisms of action, many of which have been demonstrated to play a role in autism. Scientific data have made it clear that various reasonable mechanisms exist for how vitamin D could help children with autism. Be it via anti-inflammatory actions, anti-auto-immune activities, upregulation of neurotrophins, or stimulation of antioxidant pathways, adequate doses of vitamin D (enough to obtain natural levels of **50-80 ng/mL**) may be a potential treatment for some cases of autism. ●

If you have any questions on the scientific content of this article, please call a Life Extension® Health Advisor at 1-866-864-3027.

For further information, please contact:

John Cannell, MD
1411 Marsh Street, Suite 203
San Luis Obispo, CA 93401
805-439-2569
autisminfo@sloim.com
<http://sloim.com/autism/>

References

1. de Borst MH, de Boer RA, Stolk RP, Slaets JP, Wolffenbuttel BH, Navis G. Vitamin D deficiency: universal risk factor for multifactorial diseases? *Curr Drug Targets*. 2011 Jan;12(1):97-106.
2. Carlberg C, Seuter S, de Mello VD, et al. Primary vitamin D target genes allow a categorization of possible benefits of vitamin D supplementation. *PLoS One*. 2013 Jul 29;8(7):e71042.
3. Available at: <http://www.genome.gov/27551473>. Accessed October 9, 2013.
4. Cannell JJ. Autism and vitamin D. *Med Hypotheses*. 2008;70:750-9.
5. Cannell JJ. On the aetiology of autism. *Acta Paediatr*. 2010 Aug;99(8):1128-30.
6. Available at: http://www.lef.org/magazine/mag2009/apr2009_The-Link-Between-Autism-and-Low-Levels-of-Vitamin-D_01.htm. Accessed October 9, 2013.
7. Available at: <http://www.psychologytoday.com/blog/evolutionary-psychiatry/201104/autism-and-vitamin-d>. Accessed October 9, 2013.
8. Available at: <http://www.scientificamerican.com/article.cfm?id=vitamin-d-and-autism>. Accessed October 9, 2013.
9. Kinney DK, Barch DH, Chayka B, Napoleon S, Munir KM. Environmental risk factors for autism: do they help cause de novo genetic mutations that contribute to the disorder? *Med Hypotheses*. 2010 Jan;74(1):102-6.
10. Ko ovská E, Fernell E, Billstedt E, Minnis H, Gillberg C. Vitamin D and autism: clinical review. *Res Dev Disabil*. 2012 Sep-Oct;33(5):1541-50.



11. El-Ansary A, Al-Ayadhi L. Neuroinflammation in autism spectrum disorders. *J Neuroinflammation*. 2012 Dec 11;9:265.
12. Depino AM. Peripheral and central inflammation in autism spectrum disorders. *Mol Cell Neurosci*. 2013 Mar;53:69-76.
13. Guillot X, Semerano L, Saidenberg-Kermanac'h N, Falgarone G, Boissier MC. Vitamin D and inflammation. *Joint Bone Spine*. 2010 Dec;77(6):552-7.
14. Olliver M, Spelmink L, Hiew J, Meyer-Hoffert U, Henriques-Normark B, Bergman P. Immunomodulatory effects of vitamin D on innate and adaptive immune responses to *Streptococcus pneumoniae*. *J Infect Dis*. 2013 Nov;208(9):1474-1481. Epub 2013 Aug 6.
15. Baeke F, Takiishi T, Korf H, Gysemans C, Mathieu C. Vitamin D: modulator of the immune system. *Curr Opin Pharmacol*. 2010 Aug;10(4):482-96.
16. Krishnan AV, Feldman D. Molecular pathways mediating the anti-inflammatory effects of calcitriol: implications for prostate cancer chemoprevention and treatment. *Endocr Relat Cancer*. 2010 Jan 29;17(1):R19-38.
17. Tamiji J, Crawford DA. The neurobiology of lipid metabolism in autism spectrum disorders. *Neurosignals*. 2010;18(2):98-112. Epub 2011 Feb 4.
18. Liu X, Nelson A, Wang X, et al. Vitamin D modulates PGE2 synthesis and degradation in human lung fibroblasts. *Am J Respir Cell Mol Biol*. 2013 Aug 13.
19. Ziats MN, Rennert OM. Expression profiling of autism candidate genes during human brain development implicates central immune signaling pathways. *PLoS One*. 2011;6(9):e24691.
20. Chen Y, Zhang J, Ge X, Du J, Deb DK, Li YC. Vitamin D receptor inhibits nuclear factor κ B activation by interacting with I κ B kinase protein. *J Biol Chem*. 2013 Jul 5;288(27):19450-8.
21. Available at: <http://autoimmune.pathology.jhmi.edu/faqs.cfm>. Accessed October 10, 2013.
22. Singh VK, Rivas WH. Prevalence of serum antibodies to caudate nucleus in autistic children. *Neurosci Lett*. 2004 Jan 23;355(1-2):53-6.
23. Cabanlit M, Wills S, Goines P, Ashwood P, Van de Water J. Brain-specific autoantibodies in the plasma of subjects with autistic spectrum disorder. *Ann N Y Acad Sci*. 2007 Jun;1107:92-103.
24. Mostafa GA, Al-Ayadhi LY. Increased serum levels of anti-ganglioside M1 auto-antibodies in autistic children: relation to the disease severity. *J Neuroinflammation*. 2011 Apr 25;8:39.
25. Goines P, Haapanen L, Boyce R, et al. Autoantibodies to cerebellum in children with autism associate with behavior. *Brain Behav Immun*. 2011 Mar;25(3):514-23.
26. Mostafa GA, Al-Ayadhi LY. Reduced serum concentrations of 25-hydroxy vitamin D in children with autism: Relation to autoimmunity. *J Neuroinflammation*. 2012 Aug 17;9(1):201.
27. Neveu I, Naveilhan P, Jehan F, Baudet C, Wion D, De Luca HF, Brachet P. 1,25-dihydroxyvitamin D3 regulates the synthesis of nerve growth factor in primary cultures of glial cells. *Brain Res Mol Brain Res*. 1994 Jul;24(1-4):70-6.
28. Orme RP, Bhargal MS, Fricker RA. Calcitriol imparts neuroprotection in vitro to midbrain dopaminergic neurons by upregulating GDNF expression. *PLoS One*. 2013 Apr 23;8(4):e62040.
29. Holtzman DM, Mobley WC. Neurotrophic factors and neurologic disease. *West J Med*. 1994 Sep;161(3):246-54.
30. Garcion E, Thanh XD, Bled F, et al. 1,25-dihydroxy vitamin D3 regulates gamma-glutamyl transpeptidase activity in rat brain. *Neurosci Lett*. 1996 Oct 4;216(3):183-6.
31. Garcion E, Wion-Barbot N, Montero-Menei CN, Berger F, Wion D. New clues about vitamin D functions in the nervous system. *Trends Endocrinol Metab*. 2002;13(3):100-5.
32. Sears ME. Chelation: harnessing and enhancing heavy metal detoxification--a review. *ScientificWorldJournal*. 2013 Apr 18;2013:219840.
33. James SJ, Slikker W 3rd, Melnyk S, New E, Pogribna M, Jernigan S. Thimerosal neurotoxicity is associated with glutathione depletion: protection with glutathione precursors. *Neurotoxicology*. 2005 Jan;26(1):1-8.
34. Halicka HD, Zhao H, Li J, Traganos F, Studzinski GP, Darzynkiewicz Z. Attenuation of constitutive DNA damage signaling by 1,25-dihydroxyvitamin D3. *Aging (Albany NY)*. 2012 Apr 11.
35. Heaney RP. Assessing vitamin D status. *Curr Opin Clin Nutr Metab Care*. 2011 Sep;14(5):440-4.

