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Vitamin D and autism, an update

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Vitamin D and autism, what's new?

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Abbreviations: 25(OH)D: 25-hydroxyvitamin D; ASD: autism spectrum disorder; CARS: Childhood Autism Rating Scale; calcitriol: 1,25(OH)D_2

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Abstract

An overwhelming amount of evidence point to the possibility that gestational and early childhood vitamin D deficiencies cause some cases of autism. Vitamin D is metabolized into a seco-steroid hormone that regulates about 3,000 of the 26,000 genes in the coding human genome. It is also a neurosteroid that is active in brain development, having effects on cellular proliferation, differentiation, calcium signaling, neurotrophic and neuroprotective actions; it also appears to have an effect on neurotransmission and synaptic plasticity. Children who are, or who are destined to become, autistic have lower 25(OH)D levels at 3 months of gestation, at birth and at age 8. Two open label trials found high dose vitamin D helps about 75% of autistic children with about 50% of the children having a Childhood Autism Rating Scale (CARS) below 30 after treatment. The vitamin D doses used in the first study was 300 IU/KG/day up to a maximum of 5,000 IU/day [highest final level was 45 ng/ml) while the other study used 150,000 IU/month as well as 400 IU/day (highest final level was 53 ng/ml, which is in the mid to lower third of the 25(OH)D reference range of 30 – 100 ng/ml)]. These two open label trials were recenty confirmed with randomized controlled trial used 300 IU/kg/day, which resulted in effects similar to the two open label studies. In terms of prevention, a recent study showed vitamin D supplementation during pregnancy (5,000 IU/day) and during infancy and early childhood (1,000 IU/day) significantly reduced the expected incidence of autism in mothers who already had one autistic child (from 20% to 5%). Evidence based medicine requires practitioners make treatment decisions based on the best science available. Vitamin D is safe, for example, over the last 15 years, Poison Control reports there have been approximately 15,000 reported cases of vitamin D overdose. However only three people developed clinical toxicity and no one died. 3,000 people died from acetaminophen overdose during those same years. Given those facts, I suggest practitioners should treat autism with high doses of vitamin D (300 IU/kg/day) and seek to prevent autism by supplementing pregnant women (6,000 IU/day) and infants and young children (150 IU/kg/day). As the American Academy of Pediatrics recommends vitamin D supplementation during childhood, practitioners who do not prescribe vitamin D, leave themselves open to malpractice suits for failure to prevent autism.

Vitamin D and autism, what's new?

Introduction

An epidemic of autism appears to be underway in the United States, reminiscent of another epidemic that swept Europe 250 years ago, with young children as the almost exclusive victims of its devastating effects.[1, 2] That earlier disease was vitamin D deficient rickets. Until recently it was an almost unheard of condition among children in affluent countries. Now the prevalence of rickets is rapidly growing in the United States as evidenced by findings reported in the *Mayo Clinic Proceedings.*[3]

The other disease that is rapidly growing is Autism Spectrum Disorder [ASD], which is a common neurodevelopmental disorder characterized by impaired communication and repetitive behaviors. It has recently shown a dramatically increased prevalence, (see figure 1) caused by either improved surveillance, diagnostic substitution, over-diagnosis and/or a true increase in prevalence. ASD is now diagnosed in 1 of every 64 American children by the age of eight years according to the CDC. Scientists are desperately searching for something that will both reduce the incidence and effectively treat ASD.

Until now, the cause (s) of most autism was unknown. Multiple genetic and environmental factors have been hypothesized as possible etiologies, but nothing exists to prevent or treat the core symptoms of the disorder, until now. I believe vitamin D deficiency in utero and in early childhood is the cause of a significant percentage of ASD. Vitamin D deficiency was first hypothesized to cause ASD as far back as 2007.[4] High doses of vitamin D were first proposed to have a significant treatment effect on the core symptoms of autism in 2013.[5]

A few of the possible mechanisms of action that explain vitamin D helping prevent and treat ASD have recently been reviewed. [6, 7] They include reducing risk and severity through anti-inflammatory effects in the brain, enhancing DNA repair mechanisms, anti-autoimmune effects, raising seizure threshold, increasing T-regulatory cells, protecting neural mitochondria and up-regulating glutathione, the master antioxidant, which scavenges oxidative by-products.[6, 8] Another mechanism is through vitamin D's effect on serotonin via direct genetic regulation of serotonin's rate limiting enzymes, both peripheral tryptophan hydroxylase (TPH)1 and central TPH2. Activated vitamin D (a steroid hormone) down-regulates TPH1), while up-regulating TPH2, thus explaining the serotonin paradox in ASD in which peripheral serotonin is increased but central serotonin is decreased.[9]

A resurgence of vitamin D deficiency due to sun avoidance may now be threatening our children's health, as well as that of most adults. [10, 11] a 2015 Dutch study of 6100 young children found only 33 % had adequate levels. Even

among professional basketball players, the prevalence of 25(OH)D < 30 ng/ml is 79%.[12] But according to several respected leaders in child and adult nutrition from across the United States, the current increase in autism spectrum disorders (ASD) may well be a direct consequence of significant vitamin D deficiencies in pregnant women as well as their infants and toddlers, as outlined in an extensive and excellent recent review in *Nutrients*.[13] This insidious deficiency is readily remedied – yet tragically often missed. This review will outline what's new and examine evidence that vitamin D supplementation, in high enough doses) during pregnancy and/or early childhood will decrease the incidence of autism, and remarkably, show whether high dose vitamin D is an effective treatment for some autistic children.

ASD

ASD involves poor social and verbal functioning accompanied by repetitive or "stereotyped" behavior.[14] Symptoms begin sometime in early childhood – just where the defects are and what causes them were still unknown, until now though both immune, genetic and environmental factors (air pollution, cloudy weather, seasonal factors, migration of dark-skinned immigrants to poleward latitudes, birth order, gestational diabetes, autoimmune disease in the family and nutrition), seem to play roles.[15, 16] All of the above risk factors can be explained by vitamin D, for example the mother's vitamin D levels are surely depleted by multiple pregnancies and lactation; the recurrence risk for familial ASD is 14.4% for an inter-birth interval of 18 months or less, compared with 6.8% for an interval of 4 years or more. [17] Likewise, gestational vitamin D deficiency was associated with a 2.66-fold risk for gestational diabetes. [18]

Also, several different comorbidities of ASD, [19] such as seizures and GI problems are treatable with vitamin D. [20, 21] In fact, until now, practically the only thing we knew for sure was how little we actually know about this puzzling, multi-faceted, and tragic condition, which ranges in severity from very subtle alterations in social behavior to full-blown developmental deterioration and intellectual impairment that may result in placement in long-term care facilities. ASD is a challenging condition to treat.[22]

What is undeniable is that there has been a marked increase in the number of children being diagnosed with autism over the past 3 decades,[13] not just in the U.S. but in most industrialized nations (see Figure below, which show the number of ASD cases in Indiana schools over last 14 years). While some experts argue that this rise is merely due to better detection, I can't believe parents, pediatricians and schoolteachers of the 1970s missed children with autism since most autism is not a subtle condition. Most agree that some of the increase is real, and probably represents an interaction between genes and something in the environment, something that has changed over the last 30 years.

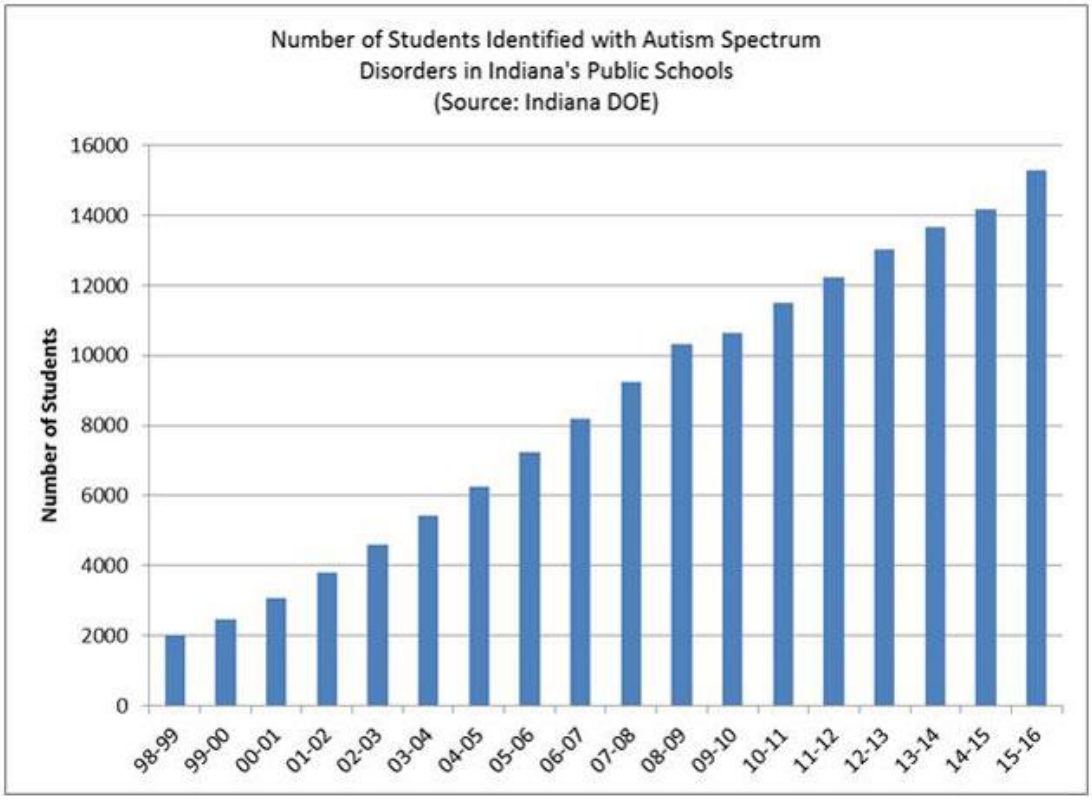

Figure 1. Increase is the prevalence of ASD in Indiana School from 1998 to 2016

What is causing this dramatic rise in autism? Studies show it is more common in urban than rural areas, in cloudy and rainy areas, in areas that get the least solar UVB and in areas with air pollution.[4] As buildings, buildings, clouds and air pollution all reduce surface UVB, they are all consistent with the vitamin D theory.[4]

As the answers have been elusive, it generated heated controversy among (and between) physician groups, other scientists and many parent groups who cling to the disproved theory that vaccines cause autism. Considerable attention has been given to mercury vaccines and other environmental toxins that cause oxidative stress; but the amount of mercury in childhood vaccines has decreased dramatically as ASD has risen, making this an unlikely culprit. For a detailed review of environment agents that have been associated with ASD, see Sealey et al.[23] Also, a recent study could not find any association between mercury levels during pregnancy and subsequent disorders in the child.[24] The same study showed there a difference in mentation of the offspring of fish-eating mothers versus fish-avoiding mothers; fish contains both omega-3 fatty acids and vitamin D.

The "Vitamin D Theory" of ASD

What possible factors involving both genetic and environmental interactions could be responsible? Is there an environmental trigger that interacts with genetic factors that may cause ASD? Such an environmental factor must not only trigger ASD, but also account for some of the dramatic increase in autism rates in the last 30 years. Our genes can't change that fast (although our epigenetics might). While our environment is clearly being altered by multiple substances, few serious scientists suggest that changes in gene function alone could cause the epidemic of brain dysfunction that has taken place in the past 3 decades.

I think the best candidate is one that has both genetic and environmental influences; one that is influenced by both nature and nurture. Our behavior has indeed undergone significant changes – changes that, because of their effects on the vitamin D neurosteroid system, can account for many of the observed facts about the autism epidemic. The most important behavior, is that over the last 30 years, Americans are avoiding the sun.

But what has happened in the past 30 years that effects the neurosteroids, which control brain development? To the best of my knowledge, only one neurosteroid has been altered over the last 30 years: calcitriol. In 1970s sunblock was rare, pregnant women were encouraged to sun bathe, mothers did not keep their children inside for fear of a sexual predator and video games were unknown. Now we are sun-phobic, lather sunblock on our kids and often put them in front of a video game to keep them inside and away from strangers. As a result, our relationship with the sun has resulted in decreased 25(OH)D.[25] This is further confirmed by a study that found the mean cord blood of 460 infants in the Boston Birth Cohort was only 14 ng/ml.[26]

The sun phobia and sunblock use is mainly the result of the 1989 American AMA Council on Scientific Affairs report, which counseled Americans against sun exposure, but did not include a word about vitamin D. [27] They did not recommend Americans take vitamin D supplements to make up for what the sun was no longer making in the skin. In fact, in 2001, researchers at the Centers for Disease Control reported, "In summary, protection from sun exposure is reported for a high proportion of children."[28] That is, the sun scare has worked. Couple this with our movement from playing outside to television and video games, and the fear modern mothers have to let their child roam around the neighborhood, and you have the "perfect storm" for the development of deficiency in vitamin D in early childhood. [29]

In a mostly white cohort in Iowa, 70% of 4 month-old breastfed infants had 25(OH)D <12 ng/ml (range 30-100 ng/ml).[30] The prevalence of low vitamin D was 50% in summer and 79% in the winter. Fifty-seven percent of infants who were followed for six months still had vitamin D deficiency. In another study from Cincinnati, 18% of exclusively breastfed infants aged 1 month had vitamin D levels <10 ng/ml; 76% of the infants and 17% of their mothers had serum 25(OH)D <20 ng/ml. [31]

There is a lot of controversy about what 25(OH)D levels are ideal, with the 2010 Food and Nutrition Board stating 20 ng/ml is adequate. The Endocrine Society says levels of 40 – 60 ng/ml are ideal. In the past, adequate vitamin D levels have been defined with a biomarker, parathyroid hormone, which tends to be elevated when 25(OH)D levels are low. However, I think there is a better biomarker, the 25(OH)D levels lactating mothers need to provide adequate amounts of D to their suckling infants. The fact that most human breast milk has little to negligible vitamin D is probably a function of most mothers being vitamin D deficient themselves. The problem is so widespread, Danish authors, after studying the D content of breast milk, recently concluded, "exclusively breastfed infants received <20% of the daily dose recommended of vitamin D recommended by the Institute of Medicine for infants during the first year of life."[32]

Levels of vitamin D in most people in modern industrialized countries are known to be much lower than those of fully sun-exposed individuals.[33] Thus, our *behavior* has had the paradoxical and unintended consequence of reducing our children's levels of a vital neurosteroid hormone that, in turn, can influence the very organ of behavior itself, the brain.[4]

What's the evidence to support the vitamin D deficiency theory? A recent (2016) 35 page review provides a substantial and cogent evidence base, that vitamin D is involved with autism starting with the characteristics of the vitamin D neurosteroid system itself.[13] Calcitriol acts as a "molecular switch" in brain tissue, turning on genes that influence brain development. In fact, vitamin D helps regulate about 3% of the genes in the 26,000 genes in the coding human genome. [34] But unlike any other vitamin system, the bulk of human vitamin D stores (80% or more) have historically come, not from oral intake, but from skin production via sunlight.

As I wrote in 2008, "Large populations of pregnant women putting small amounts of vitamin D in their mouths – in the form of prenatal vitamins – instead of generating large amounts in their skins, is novel to human brain development."[4] Since we no longer receive as much sun exposure as we did 3-4 decades ago, we need to pay closer attention to how much vitamin D we do get through our mouths. 25(OH)D levels have been falling [35] as sun protection for children has been increasing. [36]

The case for high dose oral supplementation (5,000 IU/day) for healthy people is made when one considers that skin production of vitamin D is so remarkable and robust. In fact, just 20 minutes of summer sunbathing (10 minutes on each side) at solar noon by a fair-skinned adult, produces about 20,000 units of vitamin D within 24 hours.[37] To get the same amount orally, a pregnant woman would have to drink 200 glasses of milk at 100 IU per glass (and risk fluid intoxication)

or take 50 standard prenatal multivitamins, which contain 400 IU per tablet, (and risk vitamin A intoxication) to receive the same input as the sun.

Most Americans have assiduously avoided sun exposure for the past 30 years, dutifully following AMA guidelines. Over the years more and more children are avoiding the sun, holed up in the basement playing video games and have sunblock lathered on them when and if they go outside. It is precisely during that same 30-year period that we've seen the rapid rise in autism rates, though thousands of other environmental changes occurred during this same time and such associations, on their own, mean little.

Though most people (sadly including many physicians) still associate vitamin D deficiency only with bone disease, we now understand that the seco-steroid downstream metabolite of vitamin D, 1,25 $(OH)_2D$ (calcitriol), is a neurosteroid hormone, directly responsible for many elements in brain development and behavior. Other examples of neurosteroids include estrogen, testosterone and cortisol, which have effects on many organs and also affect human behaviors. Orally ingested vitamin D is actually a “pre-hormone,” which must be metabolized by the liver into 25-hydroxy vitamin D [25(OH)D], which then forms calcitriol, the potent neurosteroid that helps control brain cell growth, and acts on vitamin D receptor molecules found in most brain cells from the very first days of embryo formation. For example, Huang et al, recently wrote “We suggest that calcitriol can be used to alleviate neuro-inflammation in various brain injuries.” [38]

Because of these potent effects, researchers in 2001 labeled vitamin D the "neglected neurosteroid" and concluded that vitamin D deficiency "should be examined in more detail as a candidate risk factor" for neurodevelopmental disorders such as autism. [39] Researchers have also opined that vitamin D, acting as a neurosteroid, offers "neuroprotection, antiepileptic effects, immunomodulation, (impact on) several brain neurotransmitter systems and hormones as well as regulation of behaviors", stressing "the importance of prenatal, neonatal and postnatal vitamin D supplementation for normal brain functioning.” [40]

But there are plenty of additional persuasive arguments supporting the vitamin D theory of autism. The calcitriol neurosteroid hormone system is different from all the body's other steroid hormone systems. While other steroid hormones are produced directly from the body's own natural store of “precursor” compounds, such as endogenous cholesterol, the amount of calcitriol produced is completely dependent on 25(OH)D availability, which in turn entirely depends on our behavior. No other steroid hormone is so dependent on human behavior.

So human behavior, be it the step into the sun, the step to the supplements, the step into the shade, or the step to the sunscreen, directly determine brain calcitriol levels. In the case of the human fetus, as we're about to see, the vitamin D neurosteroid calcitriol is directly linked to very early cognitive

development; its presence has tremendous implications for the developing baby's brain.

Genetics

Genetic factors in ASD are very important, as demonstrated by high rates of occurrence in other family members, particularly in twin studies. Today's consensus, such as it is, posits that a genetic and environmental interaction is causing ASD. For a recent review of the genetics of ASD, see Shailesh et al.[41] What is not generally known is that a meta-analysis of 11 studies found children with ASD have much lower 25(OH)D levels than did controls. [42] That these differences are important is supported by the fact that 1st trimester mothers of autistic individuals also have lower 25(OH)D and that autistic individuals have significantly lower 25(OH)D at birth (both discussed in detail below).

A recent study showed ASD is strongly associated with polymorphisms of the genes that code for the vitamin D receptor, which are associated with both lower vitamin D levels and ASD.[43] Others have found that a number of polymorphisms of the genes of vitamin D's metabolic pathway are associated with ASD (odds ratio up to 6).[44] Common vitamin D metabolic polymorphisms predict significantly lower vitamin D levels in healthy Danish children and adults.[45]

Also, in a study of siblings who were discordant for ASD, researchers found that the ASD siblings had lower 25(OH)D levels at birth than the unaffected siblings, showing ASD individuals are born with significantly lower vitamin D levels. [46]

Very recently, researchers in China found the lowest quartile of 25(OH)D levels of women in their first trimester were associated with a fourfold risk of ASD in the subsequent offspring. [47] In the same study, higher levels of 25(OH)D were associated with decreasing severity of ASD (R=-0.302, P = 0.001). Maternal 25(OH)D in the lower 3 quartiles (1, 2, 3) compared to the highest quartile (4) was associated with increased odds of ASD diagnosis in offspring: [Odds Ratio (OR), Q1: OR = 3.99, (P=0.001); Q2: OR = 2.68, (P=0.006); Q3: OR = 1.36, (P=0.25)].

The above studies imply that at least some of the genes that code for vitamin D's metabolic pathways interact with vitamin D in the environment to influence the ASD phenotype. Ambient vitamin D overcomes genetic influences as evidenced by a study of 510 Vietnamese twins. [48] In this study, the heritability of 25(OH)D was found to be 70% in the winter (other studies have found a lower heritability) but during the summer 25(OH)D became 100% environmentally determined. As the authors said, "Serum 25(OH)D concentrations are highly heritable during the winter season only. In the summer, environmental conditions (e.g., sun exposure) prevail over genetic backgrounds in determining serum 25(OH)D concentrations."

It appears likely that vitamin D is both the long sought environmental and genetic factor that interacts to determine the ASD phenotype. If one is born with the genetic tendency for ASD, that tendency may interact with environmentally or genetically controlled low 25(OH)D, as the above studies imply. The result of such inheritance is low 25(OH)D, starting in the first trimester, continuing at birth and early childhood, as shown by the decreased 25(OH)D levels in ASD children. However, the studies below imply that adequate amounts of vitamin D during gestation (6,000 IU/day) and early childhood (100 IU/lb/day) will prevent most ASD by overcoming the significant heritability of 25(OH)D levels.

Xenobiotics and CYP3A4

Examples of xenobiotics include drugs, pesticides, cosmetics, flavorings, fragrances, food additives, industrial chemicals and environmental pollutants. Humans are exposed to thousands of xenobiotics in their lifetimes. And there are numerous toxins associated with autism; for a review see Lanphear et al. [49]

What about the apparent importance of xenobiotics causing ASD? For example, does air pollution cause autism? Does the vitamin D theory explain the multiple studies showing air pollution is associated with autism? [50, 51, 52] Air pollution is now known to dramatically reduce vitamin D produced from the UVB in sunlight. [53, 54] Furthermore, if air pollution caused autism, wouldn't the epidemic have occurred during the 1950s and 60s when air pollution was much worse? Perhaps the difference is that "in the day" we were weaned on vitamin D enriched cow's milk and played in the sun. Toddlers today are deprived of sunlight and are weaned on unfortified fruit juice. [55]

So how does your body rid itself of xenobiotics, which include toxins? Often via the CYP3A4 system, a cytochrome P450 enzyme. CYP3A4 is mainly involved in cellular detoxification and it is directly genetically upregulated by vitamin D. [56] So, vitamin D activates the CYP3A4 detoxification process but vitamin D deficient autistic children cannot fully upregulate the gene and thus their brain is at risk from xenobiotics. Likewise, the body's master antioxidant, glutathione, is also upregulated by vitamin D. [57]

Immune function

Autistic individuals have abnormalities in immune functions similar to those affected by vitamin D, such as increased inflammatory cytokine levels.[58] And we know that much of the ongoing inflammation in autistic brains is the result of oxidative stress, [59, 60] just where vitamin D's powerful anti-inflammatory properties are most useful (and most critical).[61] Regardless of the cause of the autoimmune inflammatory state, vitamin D supplementation of the infants and children is very likely to help. Vitamin D up-regulates production of dendritic (peacemaker) lymphocytes that reduce the intensity of autoimmune attack by up-regulating interleukin-10, an anti-inflammatory cytokine.[62]

Calcitriol protects brain tissue by reducing inflammatory cytokine levels,[63] which, when elevated, are strongly associated with cognitive impairment in ASD. [64] Calcitriol also protects brain tissue by stimulating production of neurotropins, chemicals that combat toxicity from a number of sources, including toxic levels of intracellular calcium.[65] Very recently, a RCT found vitamin D (4,000 IU/day) significantly increased total antioxidant capacity and total glutathione levels in pregnant diabetic women (P<0.01).[66] See Figure 1.

(I will send you the graph that goes here)

Figure 1. Effect of different doses of vitamin D supplementation on oxidative stress, as assessed by (A) total antioxidant capacity and (B) glutathione levels, in patients with gestational diabetes mellitus. Data are presented as mean ± standard deviation. **P<0.01 vs. control.

The five/one male/female ration in ASD

The fact that vitamin D metabolism differs markedly under the effects of the sex hormones may go a long way towards explaining yet another puzzling fact about autism, namely its strong predilection for boys over girls. For example, researchers in Sweden have shown that estrogen has effects on developing brain tissue that serve to make it more responsive to the neuro-hormonal growth-stimulating effects of calcitriol – results which suggest that estrogen can enhance the beneficial effects of vitamin D on the brain.[67] Injection of estrogen in quall resulted in significant increases of calcitriol. [68] Women taking estrogen have 20% higher 25(OH)D as do controls.[69] At the same time testosterone significantly inhibits CYP27B1 (gene that activates vitamin D) while stimulating CYP24A1 (gene that degrades calcitriol) expression in cultured trophoblasts. [70]

Though complex, these studies do support the notion that the developing brain of a female fetus, with its higher estrogen levels, could make more efficient use of available vitamin D than would the brain of a male fetus, with its higher testosterone levels. In a situation where there was plenty of vitamin D present, such differences would go unnoticed - but introduce the all-too-prevalent maternal and early childhood vitamin D deficiency states, and the stage is set for ASD in boys but a lower incidence in girls, which is of course precisely the situation we see with autism's gender discrimination.

Exposure to UV Light – Another Clue?

We know that certain brain diseases, such as multiple sclerosis, are much more common in high latitudes where sunlight is scarce, and many scientists suspect that those conditions are directly related to chronic or seasonal vitamin D deficiencies. Significant positive association between latitude and the prevalence

of autism has recently been reported.[13] A 2013 study confirmed that children who live in low UVB light have almost three times the prevalence of ASD compared to children who live in sunny areas.[71]

One might expect that babies born in late winter would have higher rates of autism if vitamin D deficiency were involved, since their mothers would have spent most of their pregnancies in fairly low-sunlight settings. One detailed review of this topic concluded most studies find a late winter increase in autism births. [13]

If adequate amounts of vitamin D prevent autism, one would expect children with rickets to have an increased risk of autism. At least two old papers have addressed it, [72, 73] both published before Kanner described autism in 1943. Both papers describe "weak mindedness," "feeble minds," "mental dullness," "odd introverted behavior," unresponsiveness and developmental delays.[74] Even more intriguing, both papers report that the mental condition in rachitic children improved with vitamin D. More recently, a 2015 study of 35 rachitic children found 25% of the rachitic children also had autism as detected by autism ratings scales.[75]

Interventional studies

A recent propionic acid induced toxic rat model of ASD reported that vitamin D, in amounts comparative to high-dose human ones, exerted both a protective and treatment effect, with the protective effect more robust than the treatment effect.[76]

A case report in *Pediatrics* described a child with both rickets and autism. Remarkably, his autism essentially went away after his rickets was treated with 150,000 IU/month as well as 400 IU/day. **[77]** A 3-month Egyptian study of 122 subjects with ASD, found serum 25(OH)D levels were inversely correlated with severity on the Childhood Autism Rating Scale (CARS) with ($R=0.5$ and $p<0.001$). [78] An open label trial of high-dose vitamin D (300 IU/kg/day up to a maximum of 5,000 IU/day) in 83 of those 122 subjects with ASD found significant clinical improvement (mean CARS went from 37 to 30). Approximately 75% of the 83 supplemented ASD children improved ($P<0.05$) with no evidence of toxicity. In fact, the highest 25(OH)D level in these children after 3 months of 300 IU/kg/day was 45 ng/ml (range 30-100 ng/ml). The five ASD children whose final 25(OH)D was > 40 ng/ml had the most robust improvement on the CARS.

Another open label study of 37 children aged 3-11 years with ASD were treated for 3 months with large bolus doses (150,000 IU/month given intramuscularly) together with 400 IU/day by mouth. They found significant vitamin D treatment effects in ASD on standardized rating scales, again with no evidence of toxicity.[79] The mean baseline level of the treatment group was 21 ng/ml. After three (3) months of high dose vitamin D, their mean 25(OH)D was 41 ng/ml with the

highest level at 55 ng/ml. After three (3) months of treatment, significant improvement were found on the Autism Behavior Checklist (P= 0.038) and the CARS (P=0.016).

Yet another open label trial of 11 children with ASD studied changes in neurotropic factors as well as changes in the Autism Behavior Checklist after administration of varying amounts of vitamin D. Only small doses of vitamin D were given and 25(OH)D >20 ng/ml was considered adequate. Nonetheless, a significant treatment effect on standardized scales was found.[80]

The first and only randomized controlled trial (RCT) of 109 ASD children ages 3-10 by an Egyptian group using 300 IU/kg/day up to a max of 5,000 IU/day has been accepted for publication (*Journal of Psychiatry and Psychology*). In this study all autistic children with 25(OH)D < 20 ng/ml were excluded from the study for ethical reasons and treated with vitamin D. Baseline 25(OH)D of the remaining 109 study children (mean age 5.4 years) was around 27 ng/ml in both arms of the study (levels the FNB says is adequate). After the 4-month study, mean 25(OH)D in the treatment group was 47 ng/ml and was unchanged in the placebo arm. The highest 25(OH)D obtained during this “high dose” treatment was 55 ng/ml, range: (30-100 ng/ml). In a per protocol analysis, the total CARS scores significantly decreased (improved) in the vitamin D group while the placebo group remained unchanged (mean treatment CARS ± SD; 30.3 ± 6.1, versus placebo 36.4 ± 6.0; p=<0.001 respectfully), again with no evidence of toxicity.[81] Approximately 50% of the children in the treatment arm no longer met the ASD diagnosis on the CARS. Younger children responded better than older children.

In terms of prevention, an open label study of 20 infants born to mothers who already had one child with ASD, found 5,000 IU/day of vitamin D given to the pregnant mothers and 1,000 IU/day to the resultant child up to the age of 3 years reduced subsequent ASD incidence to 5% instead of the 20% rate consistently reported in the literature for mothers who already had one or more autistic children.[82] The two children (5%) who developed autism in spite of the treatment had only one of two autism scales positive, and may have responded to higher doses during childhood. For example, the 300 IU/kg/day dose, as used above in the interventional studies, would be 4,500 IU/day for a 15 kg 3-year-old.

Summary

There seems to be little doubt that some of the epidemic of autism is real, and not just a fluke of over-reporting and over-diagnosis by anxious parents and physicians. There’s equal certainty that we also face an epidemic of vitamin D deficiency as we steadily move away from old ways that exposed us to more vitamin D producing sunlight. The vitamin D theory of autism has significant support. Randomized controlled trials are currently underway (one using a stock dose of only 2,000 IU/day, a dose that will not get the children’s 25(OH)D into the

40s and 50s where (in my experience) a treatment effect may be more likely. While we are awaiting those results, however, it seems prudent to maximize vitamin D status in pregnant women, infants and young children, aiming for levels found in humans living in a sun-rich environment,[83] which are between 40-60 ng/ml, which is mid-range of 25(OH)D's reference range (30 – 100 ng/ml).

In order to prevent autism, I believe pregnant and lactating women should take 6,000 IU/day.[84, 85] Children, from infants at the breast to 3-year old toddlers to 6-year-old first graders, should take 100 IU/pound/day not to exceed 5,000 IU/day unless regular 25(OH)D levels are obtained. This means that in order to prevent autism, a 20-pound child should take 2,000 IU/day and a nursing infant about 1,000 IU/day. If the lactating mother is taking 6,000 IU/day, the infant will get all the vitamin D it needs from their mother's milk but the infant should take 1,000 IU/day after weaning. We know these preventative doses are safe from the above controlled trials which used twice the dose, but only obtaining low to middle 25(OH)D levels.

To treat autism with vitamin D, it would seem wise to choose a dose we know works, that being 300 IU/kg/day with a maximum of 5,000 IU/day. As the open study above reports, only 5 children exceeded levels of 40 ng/ml at the end of the study, and the authors noted that those 5 children responded best to treatment. Even the unusual dosage regimen used in China to treat autism (1.5 million IU/month delivered intramuscularly combined with 400 IU/day for 3 months) did not result in toxicity, with the highest 25(OH)D level at 52 ng/ml.

The American Academy of Pediatrics (AAP) recommends all healthy infants up to the age of one year take 400 IU/day (10 mcg) of vitamin D and 600 IU/day (15 mcg) after the first birthday. These doses low but may help prevent some ASD. However, research has shown that about 70% of American toddlers do not take any vitamin D at all, in spite of the AAP recommendation.[86] Also, only 20% of American infants get the 400 IU/day the AAP recommends.[87] It is unknown if parents simply ignore the pediatricians advice or if pediatricians are forgetting to recommend vitamin D supplements for infants and toddlers.

Pediatricians who fail to recommend supplementation may open themselves up to malpractice suits. An autistic child would make a very sympathetic plaintiff, and the mean lifetime costs for a child with autism is about 2.4 million dollars [88] (not including non-economic damages), a sum that will attract plaintiff (malpractice) attorneys. Also, it would be wise not to rely on "standard of care" to save you. What other physicians are doing or saying is "standard care." "Standard of care" is what a reasonable physician should have done, based on the latest scientific literature.

Compliance with Ethical Standards

Funding: none

Conflict of interest: JJC is president of the non-profit Vitamin D Council; he receives remuneration from Purity.

No humans or animals were used in this study.

This article does not contain any studies with human participants performed by any of the authors.

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