

Infant Exposure to Excessive Vitamin D: A Risk Factor for Autism

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Abstract

Autism is a neurodevelopmental disorder that is normally defined by its behavioral characteristics but also often features a known biochemical gestalt. This biochemical gestalt includes a Th2 skew to the immune system, endothelial damage, oxidative stress, excessive neuronal connectivity, and dysregulated monoamines. In sufficient doses, oral supplementation with Vitamin D induces a Th2 skew to the immune system, endothelial damage, oxidative stress, excessive neuronal connectivity, and dysregulated monoamines. A number of genetic syndromes that are comorbid with autism feature excessive calcification. One of these, Williams syndrome, features hypercalcemia that is associated with elevations in blood levels of vitamin D. Vitamin D consumption among babies and toddlers in the United States is high relative to historical norms and has been increasing in recent decades coincident to the rise in autism rates. Low rates of autism have been observed among the Amish and in Cuba where there is no supplementation or fortification with vitamin D. Autism is more common among males than females and large doses of oral vitamin D are more toxic to males than females. These facts support the hypothesis that oral vitamin D consumption among the young may be a risk factor in inducing autism.

Introduction

Autism is a neurodevelopmental disorder that appears in the first three years of life. Evidence suggests that both genetics and environment play a role in inducing it [1]. In recent decades the number of autism cases has increased substantially faster than population growth, and it appears that factors such as changes in diagnostic criteria and identification of cases that previously had remained undiagnosed do not fully explain this increase [1]. Different environmental factors have been examined to account for the unexplained part of the increase. Hviid et al. examined thimerosal in vaccines [2]; Taylor, et al. examined the combination mumps-measles-rubella vaccine [3]; Shaw suggested the transition from aspirin to acetaminophen [4]; Roberts, et al. investigated organophosphate pesticides [5]; Zhou, et al. suggested early infant exposure to excess multivitamins [6], which is a more general version of this paper; and Cannell suggested insufficient vitamin D [7], which as it applies to supplementation is the opposite of this paper.

Vitamin D is a fat soluble vitamin that enhances calcium absorption, raises blood levels of calcium, and affects the immune system. It can be synthesized in the skin through sunlight and in this sense it is not a vitamin as more than enough can be synthesized from sunlight to promote good health. Vitamin D produced in this way will not result in toxicity due to self-regulating mechanisms. Vitamin D may also be absorbed orally, where there is no similar self-regulating absorption mechanism [8]. So large oral doses of vitamin D can be toxic. This is demonstrated by the fact that one can easily consume enough orally from non-natural sources that death results [9].

Methods

The hypothesis that excess vitamin D consumption is a risk factor in inducing autism will be examined from the perspectives of biochemistry, genetics, and epidemiology. The biochemical dysfunction in autism will be examined and compared to the biochemical dysfunction caused by large doses of vitamin D; some genetic syndromes that often are comorbid with autism and feature excessive calcification will be examined; and the levels of vitamin D consumed by the young in select populations will be analyzed and compared to data on the epidemiology of autism. In addition some counter arguments to the hypothesis will be considered.

Biochemistry of autism

Alton et al. and Geier et al. among others have highlighted that when one examines the biochemistry of those with autism in populations that have no obvious genetic defects, some aspects of biochemistry seem to be common [10,11]. In this section some of the biochemical characteristics of autism are highlighted.

The thymus produces many cells that help regulate the immune system. Among these cells are Th1 cells and Th2 cells. Th1 cells focus the immune system on intracellular pathogens, while Th2 cells focus the immune system on extracellular pathogens. In some diseases the immune systems is skewed toward Th1 cells, in others it is skewed toward Th2 cells, and in others there is no skew [12]. Gupta found that there is a significant imbalance toward Th2 in autism relative to controls [13].

Yao, et al. found that autism also features endothelial damage: each of these metabolites is elevated in the urine of those with autism relative to controls: isoprostane F_{2α}-VI; 2,3-dinor-thromboxane B₂; and 6-keto-prostaglandin F_{1α}. These markers and particularly the latter are markers for endothelial damage [14].

James, et al. found that autism features high levels of oxidative stress: in autism there are lower levels of blood plasma metabolites S-adenosyl methionine (SAM), methionine, cystathionine, cysteine, and total glutathione and significantly higher levels of S-adenosyl homocysteine (SAH) and oxidized glutathione relative to controls. Collectively these markers indicate oxidative stress [15].

Supekar, et al among others has highlighted that autism often features excessive neuronal connectivity in the brain [16].

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Martineau, et al., among others has highlighted that autism features dysregulation of catecholamines including dopamine and its derivatives homovanillic acid and 3-4 dihydroxyphenylacetic acid [17]. For this reason some have suggested using dopaminergic drugs in some cases of autism [18].

Some biochemical effects of excessive vitamin D consumption

Cantorama, et al. found that oral consumption of vitamin D induces a Th2 skew to the immune system [19]. Hypponen, et al. found that oral vitamin D supplementation early in life is associated with higher rates of allergies, asthma, and atopic dermatitis in later life [20]. Kull, et al. confirmed vitamin D supplementation early in life is associated with higher rates of allergic conditions later in life when vitamin A is supplemented as well [21]. Allergies, asthma, and atopic dermatitis all are diseases characterized by Th2 skew [22,23]. Recall that autism also features a Th2 skew.

Calcium supplementation in women is associated with elevated risk of cardiovascular events [24]. Recall that calcium and vitamin D work synergistically. Also vitamin D supplementation at a very modest dose (300 IU per day) over a long period of time has adverse effects on serum lipids during hormone replacement therapy in postmenopausal women [25]. While the supplementation levels in these trials were modest, they suggest that oral vitamin D at large doses could cause vascular issues in some populations.

In animals, large oral doses of vitamin D have been tested. In pigs they induce atherosclerosis [26]. In rats large oral doses have been used to model atherosclerosis. Other associated effects in rats are vascular calcification and endothelial damage [27]. The results from large doses in animals and hints of vascular effects from studies in human adults, suggest that large oral doses of vitamin D given to human babies could induce endothelial damage in some. Recall autism features endothelial damage.

High doses of vitamin D in rats induce oxidative stress. One set of researchers injected vitamin D into rats on a high cholesterol diet to induce atherosclerosis. They then examined the rats' aortas. Among their findings were elevated levels of oxidative stress markers [28]. Recall autism features elevated levels of oxidative stress.

High dose vitamin D consumption by rats alters catecholamines. Tekes et al. found that a single large dose of vitamin D given to baby rats produces lifelong effects on catecholamines in the brain including dopamine and its derivatives [29]. Recall autism features dysregulation of catecholamines including dopamine and its derivatives.

Vitamin D upregulates nerve growth factor and promotes neuronal overgrowth [30]. One may infer that large doses of vitamin D provided to babies would cause excess neuronal connectivity in some. Recall that autism features excessive neuronal connectivity.

These data suggest that large oral doses of vitamin D given to human babies could produce endothelial damage, oxidative stress, a Th2 skew to the immune system, vulnerability to Th2 diseases, excessive neuronal connectivity, and dysregulated catecholamines.

Genetics

There are a number of genetic syndromes that have high comorbidity with autism, and in many excessive calcium plays a role in etiology. Lu, et al. highlighted some of these [31]. Palmieri et al. noted that expression of the AGC1 gene plays a role in some cases of autism and has found that it is excessive intracellular calcium that causes the

cascade of events leading to neuronal dysfunction in these cases [32]. Timothy syndrome features comorbidity with autism of 60%, and is caused by a defect in the gene CACNA1C, which causes a delay in closing calcium channels [33]. Sotos syndrome is also often comorbid with autism and features hypercalcemia and advanced bone age [33].

The above examples suggest that excessive calcium plays a role in inducing autism in some severe genetic syndromes. While the vast majority of those with autism do not have such significant genetic abnormalities, the connection to calcium that these syndromes highlight suggests that excessive calcium could play a role in inducing autism in other cases. Therefore excessive supplementation with vitamin D, which increases calcium absorption and calcium levels in the blood, could be a risk factor in inducing autism in some.

Williams syndrome, another genetic syndrome with high comorbidity with autism, also features hypercalcemia. Comorbidity with autism has been estimated at 50% [33]. The hypercalcemia in Williams syndrome is caused by dysfunctional regulation of vitamin D levels in the blood [34]. Barnett et al. suggest that this due to a deletion of the WSTF gene [35]. For this reason oral supplementation of vitamin D in Williams syndrome is contraindicated [36]. The excessive calcification seen in Williams syndrome as well as other genetic syndromes associated with autism suggests that the autism often seen in Williams syndrome could be due to excessive calcium and that the underlying cause may be the fluctuations in blood levels of vitamin D. This also suggests that significant fluctuations in blood levels of vitamin D may be a risk factor in inducing autism more generally.

Vitamin D consumption by the young

Oral vitamin D consumption by babies and toddlers in the United States is high relative to what is available in breast milk and high by weight relative to what adults consume. There is very little vitamin D in most foods, and almost none in human milk. Dietary Reference Intake for vitamin D is 400 IU for babies. So to achieve this level, the American Academy of Pediatrics recommends that infants receive vitamin D through infant formula or vitamin D drops starting at birth [37].

In the United States, both cow's milk and baby formula are fortified with vitamin D (Table 1, Figure 1), and both typically have more vitamin D than what is listed on the label. In the case of cow's milk regulations require manufacturers to aim for between 100% and 150% of what is on the label. So typically the vitamin D content is about 25% higher than what is on the label [41]. Formula manufacturers typically over-fortify as well, and on average they exceed what is on the label by 37% [42]. A baby boy will consume about 570 calories per day. A baby girl will consume slightly less [43]. Similac contains 35.7 IU of vitamin D per 23.8 calories [40]. So a baby boy obtaining his sustenance from Similac formula will receive about 855 IU of vitamin D per day. If the same baby were to rely on human milk alone for its sustenance, it would receive about 30 IU per day as the amount of human milk consumed by a baby is typically less than 850 ml/day and human milk contains 33 IU of vitamin D per liter [44]. So on Similac formula the baby would get more than double the 400 IU DRI and much more than what are obtainable via human milk.

Source	Vitamin D per liter
Human milk	33 IU [38]
Cow's milk straight from cow	29 IU [39]
Cow's milk from store	428 IU [40]
Similac baby formula	1206 IU [40]

Table 1: Vitamin D in select beverages in the United States.

Babies who obtain vitamin D through droppers should in theory receive about 400 IU per day as this is the usual dose on the label. The actual amount provided may be more. Droppers are unreliable especially with a squirming baby. The FDA realized this is a danger and has issued a warning about it [45]. Some enthusiastic parents may give more than directed in the mistaken belief that they are helping their baby. A baby can get multiple doses if there is confusion about who is responsible for giving the drops. If a baby is nursed primarily by its mother and receives vitamin drops regularly as a result, but also gets some supplemental formula on occasion, this would also raise the levels of vitamin D consumed.

The dose of vitamin D that a baby receives is disproportional to an adult dose. A big newborn baby weighs about ten pounds. The weight of the average adult is about 150 pounds [46]. So by weight the 855 IU per day dose that a baby obtains via Similac formula is equivalent on an IU per pound basis to a dose of 12,800 IU per day for an adult. DRI for an adult is 800 IU per day.

Epidemiology of autism in the United States and a history of vitamin D consumption by babies

Autism rates in the United States had been fairly steady for decades until around 1980 at which point they began increasing (Figure 2). Since

1980 the amount of vitamin D consumed by the young has increased as well. The actual levels of vitamin D in baby formula likely increased, the actual levels of vitamin D in milk have increased, the availability of other vitamin D fortified foods has increased, the use of vitamin D drops has become widespread and started earlier, more formula and milk are consumed by the very young, and the vitamin D available in children's multivitamins has increased. Working against these trends has been an increase in breast feeding during this time period [47].

With respect to vitamin D consumption in the early 1980s, there is evidence that it increased among the young for two reasons: 1) vitamin D levels in baby formula likely increased due to increased regulation and fear of litigation, 2) lower fat milk consumption increased resulting in higher levels of vitamin D consumed as lower fat milk has higher levels of vitamin D per calorie. On higher vitamin D levels in formula, in 1978 a formula maker reformulated its product to remove salt. As a result some babies developed hypochloremic alkalosis and brain damage in 1979 due to lack of chloride in the formula [48]. So Congress passed the Infant Formula Act of 1980, which required certain minimum nutritional requirements for baby formula. In the case of vitamin D, it required at least 40 IU per 100 calories of baby formula. Previously this level of fortification had been a recommendation that was generally followed by the industry, but it was not enshrined in law [49]. In addition the publicity and lawsuits that came about from the incidents of metabolic alkalosis, put manufacturers of baby formula on notice that under fortification of any vital nutrient had serious repercussions. Technology for efficient testing of vitamin D levels in liquids was still being developed at that time. When testing was done in the early 1990s, all baby formulas tested had levels above what was mandated, and many had more than 100% above what was mandated [50]. This data suggests that the levels of vitamin D in formula likely increased because of this act and the additional regulatory scrutiny.

On lower fat milks, milk with 2% milk fat contains about 7% more vitamin D per calorie than whole milk and 24% more calcium per calorie than whole milk [40]. Experiments in rats show high doses of vitamin D are more toxic in diets with higher calcium content [51]. These data suggest that if there are populations susceptible to oral vitamin D consumption that 2% fat milk is more problematic than whole milk. The same argument suggests that 1% or skim milk is more problematic than 2% milk. In the early 1970s per capita consumption of lower fat (2% or lower in this context) milk in the United States was relatively low. By the late 1980s per capita consumption of lower fat milk had tripled and much of this increase occurred during the late 1970s and early 1980s [52]. In the early 1980s it was common to transition babies from formula or human milk to cow's milk at about 6 months of age. Recommendations to use human milk or formula through one year of age were made in 1992 [47]. This suggests that at least some of the increase in low fat milk consumption during the 1980s was due to consumption by babies and toddler. Indeed there is contemporary evidence that some low fat milk was consumed by the very young, and some of it caused gastrointestinal issues in the same population [53]. So if the hypothesis that vitamin D consumption is a risk factor for autism is valid, then this increase in consumption of lower fat milks by the very young would be expected to cause an increase in autism rates.

Based on data from the California Department of Developmental Services there was a more significant increase in autism rates during the 1990s as illustrated in Figure 3 [54].

In the early 1990s coincident to the increase in autism rates there was a substantial increase in the amount of vitamin D in milk with no change in the label. As highlighted previously technology for measuring

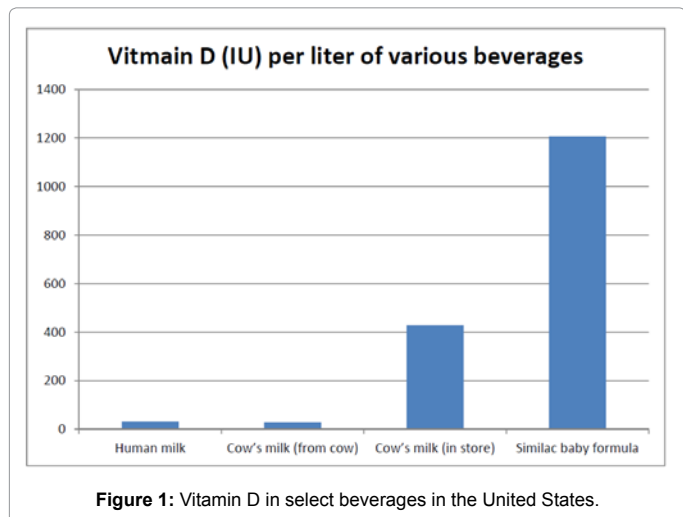
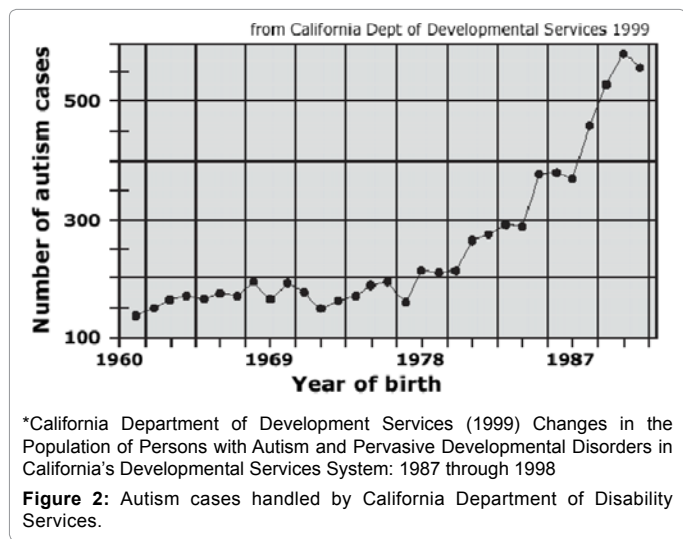
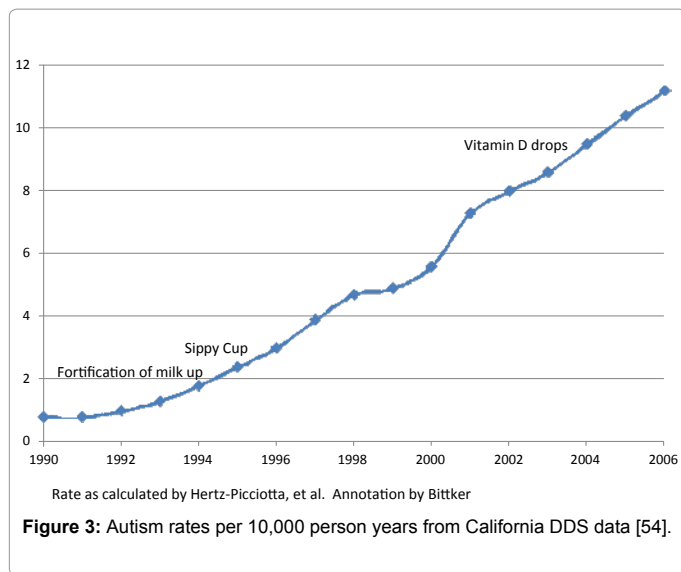


Figure 1: Vitamin D in select beverages in the United States.



*California Department of Development Services (1999) Changes in the Population of Persons with Autism and Pervasive Developmental Disorders in California's Developmental Services System: 1987 through 1998

Figure 2: Autism cases handled by California Department of Disability Services.



vitamin D content of liquids was developed in the early 1980s [55]. Using this technology studies on vitamin D supplementation of milk published between 1988 and 1992 found that in most cases the actual level of vitamin D in milk was much lower than the level listed on the label. For example a 1992 study found that only 12 of 42 samples were within 20% of what was on the label and the majority of the samples had vitamin D levels that were far below the level on the label [50]. So in December 1992 the FDA issued new guidelines that required milk manufacturers to achieve fortification levels of 100% to 150% of what was on the label, and over fortification was to start at 200% of what was on the label [56]. While samples taken early in the next decade indicate that manufacturers did not always achieve the levels mandated, they do confirm that this regulation and perhaps more aggressive enforcement as well did on average result in a dramatic increase in the amount of vitamin D in milk [41].

The increase in autism rates since the early 1990s has not stabilized yet. Oral consumption of vitamin D by the very young has continued to increase as well. Playtex introduced the Sippy cup in 1994. After reconfiguring the product in 1995, sales increased dramatically, and knock-offs quickly entered the market [57,58]. Busy parents no longer needed to supervise their children while they consumed beverages, which likely led to an increase in consumption of formula and milk and a resulting increase in consumption of vitamin D. Also a number of foods that had never previously been fortified with vitamin D are now fortified with vitamin D. For example vitamin D fortified orange juice is now ubiquitous, but it was considered a novel product in 2003 [59].

In addition DRI guidelines for vitamin D for the young have been increased and publicized by the American Academy of Pediatrics resulting in increasing consumption of vitamin D by babies. In April 2003, based on concern about rickets, the American Academy of Pediatrics published guidelines for vitamin D intake of 200 IU per day starting at two months of life and continuing until the child can obtain vitamin D from fortified milk or other sources. This recommendation included breast fed babies [60]. In November 2008 the American Academy of Pediatrics revised its guidelines to 400 IU per day starting from birth [61]. This new level was double the prior level starting at an earlier age.

Looking back further, vitamin D fortified milk and milk products

first became available in major cities of the United States beginning in the middle 1930s [62]. Kanner first described the syndrome that we now call autism in his classic paper published in 1943. Among his observations, Kanner noted that five of the eleven children he identified had severe feeding difficulties from an early age, and in some cases their parents switched formulas multiple times due to these difficulties. Kanner mentioned milk incidentally in two cases. In one the child confuses his pronouns when he asks for it. In the second the child has a special milk glass [63].

Kanner also commented that the parents of his patients were generally highly educated and successful members of the middle class [63]. It seems that these are just the type of upwardly mobile forward thinking people who would be tempted to purchase new and slightly more expensive products for the sake of their children's health: namely vitamin D fortified milk products.

Kanner had been a physician since 1921, had worked as a psychiatrist in a state hospital starting in 1924, and had been specializing in child psychiatry in the pediatric hospital at Johns Hopkins since 1930 [64]. Yet Kanner notes that 1938 was when he first started seeing this condition that differed so markedly from anything reported previously, and between when he submitted his paper and when it was published, he identified two more children with the same syndrome [64]. This set of facts suggests that many cases of autism first became apparent soon after vitamin D was added to milk products, some of Kanner's cases consumed vitamin D fortified milk products, some may have had bad reactions to those same milk products given gastrointestinal issues reported, and the timing of Kanner's discovery of autism may be connected to the introduction of vitamin D fortified milk products in the United States in the middle 1930s.

Other epidemiological evidence

The Amish population of the United States has very low rates of autism [65]. The Amish consume raw milk rather than buying milk in a store [66]. Raw milk is milk that comes straight from a cow and has not been fortified with vitamin D, and the Amish do not give their babies vitamin D supplements as they follow the old ways. Hence oral consumption of vitamin D by Amish babies is minimal. So the Amish anomaly is consistent with the hypothesis that vitamin D consumption may be a risk factor in inducing autism.

Cuba is another anomaly in autism epidemiology. Shaw observed that those with an autism diagnosis in Cuba represented 0.00168% of the population in 2012, while those with an autism diagnosis in the United States represented about 0.5% of the population in the same year [4]. Cuba is not a wealthy country, but it has one of the highest doctor-to-patient ratios in the world, and its public health system does a good job of delivering care by most metrics [67]. This suggests that Cuban medical personnel would be able to identify and report autism if it were present in the population. In Cuba vitamin D drops are not normally provided to babies [68]. Cuba also does not fortify foods with vitamin D; nor does the Cuban health service provide vitamin D through any of its fortification programs [69]. So the Cuban anomaly is consistent with the hypothesis that oral consumption of vitamin D by the young is a factor in inducing autism.

Another aspect of the autism epidemic is its gender bias: it strikes over four males for every female [70]. Toxicologists have analyzed the effect of vitamin D on rats and have learned that the LD50 of vitamin D for a male rat is 30 mg per kilogram of body weight, and the LD50 in female rats is 50 mg per kilogram of body weight [71]. From this

one may conclude that high doses of vitamin D are more toxic to males than females. So if oral vitamin D consumption is a factor in inducing autism, it would help explain autism's gender bias.

Schultz, et al. highlighted that autism disproportionately affects those who are fed formula rather than human milk as babies and that increased duration of breast feeding is associated with lower risk of autism [72]. Since vitamin D levels in baby formula are high relative to human milk and high relative to the amount in vitamin D drops from data presented in a prior section, these findings are consistent with the hypothesis that vitamin D consumption may be a factor in inducing autism.

Examining some counter arguments

Hyman, et al. among others has observed that the vast majority of those with autism consume less vitamin D than the DRI [73]. This may seem to contradict the hypothesis that excessive vitamin D consumption is a factor in inducing autism. Hyman's study examined individuals who were already affected with autism and who were between 2 and 11 years old. The biochemistry of vitamin D and its long term effects on the immune system and monoamines suggest that the crucial stage for consumption may be before or while autism is developing: not after diagnosis. From a prior section in the United States most babies who consume formula and many babies who consume vitamin D drops consume much more than DRI levels of vitamin D, and this likely holds to a greater extent in those with autism because of the higher rates of formula feeding among those who develop autism. In addition as previously noted the vitamin D DRI itself is high for babies and toddlers. So vitamin D consumption in babies and toddlers who eventually are diagnosed with autism may be high even though Hyman, et al. found low vitamin D consumption relative to DRI in those who have an autism diagnosis.

Cannell and Grant among others have suggested that insufficient vitamin D is a factor in inducing autism and Cannell has suggested oral supplementation with large doses of vitamin D to prevent autism [7,74-76]. Cannell and Grant observe autism is more common in higher latitudes with less sunlight, those with Williams syndrome with its spikes in vitamin D levels often have a phenotype in later life that is the opposite of autism, those with autism typically have lower blood levels of vitamin D than controls, and vitamin D reduces autoimmune disease, down regulates inflammation, and has antioxidant effects-all of which should reduce the risk of autism [7,74-76]. The state data that Cannell and Grant use to support the sunlight hypothesis do indeed show the highest rates of autism among the states of Minnesota and Oregon which are in the northern latitudes. Yet these states have autism rates that are much higher than Alaska's autism rate and Alaska is much farther north. In addition Texas and Florida which are in lower latitudes both have autism rates that are higher than Alaska's rate and are four times higher than Iowa's rate [77]. Hawaii, which is the nearest state to the equator, has an autism rate that is comparable to Alaska's rate, is three times higher than Iowa's rate, and is orders of magnitudes higher than Cuba's rate even though most of Cuba is on a slightly higher latitude than Hawaii is [77]. These data suggest if latitude is a factor in inducing autism it is not of great significance.

Williams syndrome supports a conclusion that is the opposite of what Cannell suggests. As previously discussed Williams syndrome features 50% comorbidity with autism and autism by definition strikes before three years of age. So Cannell's observation that those with Williams syndrome are often easy going when they are older is not as relevant to autism etiology as Williams syndrome's high comorbidity

with autism and its connection to spikes in vitamin D among the young.

Blood levels of vitamin D, if not manipulated by oral supplementation, are good markers of endothelial damage [78]. As previously highlighted autism often features endothelial damage. So the low blood levels of vitamin D seen in autism relative to controls that Cannell cites as evidence of deficiency may in some be a sign of endothelial damage. Also as previously examined endothelial damage may be caused by past supplementation with large doses of vitamin D. With respect to autoimmunity, the observation that vitamin D may be helpful in ameliorating autoimmune diseases is largely based on the fact that many autoimmune diseases feature cytokine dysfunction that is characteristic of a Th1 skew to the immune system, and vitamin D supplementation tends to lower Th1 levels and raise Th2 levels [12,19]. However, as previously highlighted in autism the usual pattern is a significant Th2 skew relative to controls. Therefore the long term effect of vitamin D supplementation in autism will not normalize the immune system as it may in some other autoimmune diseases. With respect to vitamin D down regulating inflammation and having antioxidant effects, at high doses oral vitamin D has the opposite effects as highlighted by the oxidative stress and endothelial damage seen from oral supplementation with vitamin D that are discussed in a prior section.

Conclusion

Given that 1) autism features Th2 skew to the immune system, endothelial damage, oxidative stress, excessive neuronal connectivity, and dysregulated monoamines; 2) oral vitamin D in large doses is toxic and causes Th2 skew to the immune system, endothelial damage, oxidative stress, dysregulated monoamines, excessive neuronal connectivity, and induces susceptibility to other Th2 mediated diseases; 3) the genetics of autism syndromes suggest that excess calcium and related elevations in vitamin D may be connected to its etiology in some cases; 4) babies in the United States receive large oral doses of vitamin D starting at birth; 5) autism rates in the United States have increased whenever oral consumption of vitamin D has increased; 6) the Amish and Cuba have very low rates of autism and consume no supplemental vitamin D as babies; 7) vitamin D is more toxic to males than females and autism is more common in males than females; it seems that excess vitamin D consumption by babies and toddlers could be a risk factor in inducing autism. Further studies are needed to confirm this hypothesis.

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