Role of Vitamin D and Calcium in Autism Spectrum Disorder: Overview

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Abstract

Autism Spectrum Disorder (ASD) is a heterogeneous neurodevelopmental condition that cause common problems in communication and social interactions among children. Beyond the role of vitamin D in bone metabolism, also has a critical role in brain development. Deficiency of vitamin D is related to augmented risk of neurodevelopmental complaints such as (ASD). Vitamin D could maintain the phenotypic stability of both the Ca2+ and redox signaling pathways that play such a key role throughout development.

Introduction

Autism Spectrum Disorder (ASD) is considered as a heterogeneous neurodevelopmental situation, influencing about 1% of kids [1,2]. The ASD is classified via social communication shortfalls and the existence of restricted or repetitive interests or behavior (American Psychiatric Association 2013). There are shared difficulties in social interactions and communication among children having ASD as subjects linked to behavioral challenges, comprising aggression, non-compliance and self-injury (American Psychiatric Association 2013). There is no medication can cure ASD; but selected drugs can aid address some of the symptoms related to ASD, especially certain behaviors (American Psychiatric Association 2013). Some ASD intrusions were based on behaviors, while others were deliberated food therapies that relatives trust may enhance behavioral outcomes, as minerals, vitamins, Gluten-Free & Casein-Free (GFCF) diet and essential fatty acids [3-5]. The communal criticisms of ASD individuals are abdominal pain, chronic constipation and diarrhea [6]. Certain foods cause gastrointestinal and allergies symptoms, in addition to behavioral symptoms [7]. Given the early onset and chronic nature of ASD, dietary supplements can determine the need for families, because they can be administered early or for a long time for younger children [8,9]. Autism Spectrum Disorder (ASD) is the term for a variety of circumstances, counting Asperger syndrome, that influence a person’s social communication, interaction, behavior and interests. The Centers for Disease Control and Prevention (CDC) evaluates autism’s propagation as 1 in 68 children in the United States. Autism is the greatest common in girls (1 in 42 boys vs. 1 in 189 girls). In UK, it is probable that one in every 100 persons has autism. Previously around 700,000 children in UK have autism. When Australia is painstaking, it is estimated that almost 230,000 Australians reanimate with ASD that is around four times more frequent in boys than in girls. Astonishingly, India, one of the largest countries in the World, had no exact data of prevalence of autism [10]. Symptoms are expressed in autistic children earlier the age of three. Sometimes diagnosis can be made at age of three or later. Early intrusion in those patients may progress outcomes only. ASD causes are numerous; one of them is gene influence for sure. Nevertheless, no exact genes are related with ASD. Apart of genes, definite impact can be referred to environmental influences. The greatest supposed environmental complexes registered in epidemiology that can have impact on ASD, are pesticides, tetrachlorodibenzodioxin, benzo (a) pyrene, valproate, heavy metals, bisphenol A, cocaine, acetalaminophen, polyhalogenated biphenyls, diesel constituents, phthalates, etc. Also, there are listed endocrine disruptors (over 100) including parquat, atrazine and other pesticides not yet studied in autism and many compounds used in food, cosmetics or household products (including aspartame, tretinoin, soy phytoestrogens, titanium dioxide, and sodium fluoride). Some researchers have shown that dense contact to pesticides and air pollution (especially particulate matter <2.5 and 10 μm in diameter) throughout pregnancy is also related to ASD [11]. Numerous polluting chemical materials can affect Thyroid Hormone (TH) metabolism that might lead to irregularities in the neurological development of the child or the fetus. There was connection between autism development and thyroid gland dysfunction [12]. Investigators also observed other likely related factors. They found that maternal infections (CMV and rubella with fetal brain injuries, and possibly
Influenza with fever), maternal inflammation and prolonged fever, particularly with modifications in assortment of antibodies and inflammatory cytokines that cross the placenta may lead to ASD by affecting the brain of fetus. Some drugs as: Valproic acid, misoprostol, thalidomide, etc. paracetamol and β2-adrenergic receptor agonists have also latterly been related to augmented rate of ASD however the data is too in conclusive and preliminary [13]. Forward-looking parental age is also related to higher risk of ASD. Birth complications that are associated with ischemia or trauma and hypoxia have also shown strong relations to ASD. On the other side, other pregnancy related factors as diabetes maternal & obesity, and caesarian section have shown a less strong (but significant) relationship with ASD risk. Food allergies are frequently correlating with ASD. In one case report, peanut and milk allergies were conveyed in 13 months old child [14]. There is mounting attention in the oxytocin system role in social behavior & cognition. The neuropeptide oxytocin and its receptor have been prophesied to be implicated in organizing social functioning in autism spectrum disorders. Some researchers inspected the Oxytocin level (OT) in people suffering from ASD. They found that individuals with ASD may exhibit an OT dysregulation on the basis of changes in OT receptor gene expression [15]. OT can be liberated from brain throughout stressful circumstance [16].

**Nurture and Nature**

Although there is varied recognition that ASD has double reasons, both environmental and genetic in origin, lacking of accurate conception of the precise technique supporting strange neurodevelopment. Autistic broader phenotypes and characters (subclinical) of ASD are inherited and ceaselessly dispersed in the general population, through etiologies overlapping with clinical phenotypes [17]. Genome sequencing data mentions there are hundreds of genes related to ASD, both rare and common (de novo and inherited), with several common with another psychiatric, neurodevelopmental, and neurological conditions [18]. However the clinical service of genetic proof is currently restricted, it is improving, enabling in some cases estimation of the likelihood of familial recurrence, genetic explanations of ASD, and identification of other related genetic risks [19]. Whereas heritability assessments for ASD range from 38% to 55% and upwards to 95%, some twin and family researches proposed heritability had a lesser role than supposed before, indicating a greater part for environmental factors [20-23]. While one twin study found shared environment plays a major role in ASD etiology, the majority of family and twin studies suggest non shared environmental factors, or factors unshared between family members that make them dissimilar, are more influential [23]. But, classifying exact non-shared environmental reasons is interesting given they out spread behind features of nurturing, to factors with measurement fault, random biological noise, social chance, neuroinflammation & immune reaction, also genetic and epigenetic differences in identical twins [24]. Evidence of non-shared environmental impacts has been found through the life span and autism spectrum, from autistic characters to extreme clinical phenotypes of ASD. Complicating the decoding of the impact of non-shared environmental factors in the ASD etiology is the point that their key mechanism is likely collective frequency, rather than lone causative agents [25]. As monozygotic twins share 100% of their genetic variation at a DNA sequence level and dizygotic twins share on average 50%, twin researches offer a lone prospect for designing the relative influence of genetics and environmental factors to ASD phenotypes. Comparing dizygotic and monozygotic twin pairs and their phenotypic discordance and concordance enables examination of the environmental and genetic contributions (non-shared and shared) to ASD presentations (ACE model) [26]. The environment can be both causal if it influences the causal chain between a genetic predisposition and ASD, mediating if it is harmful and precedes ASD, protective if it decreases the risk of ASD and moderating if it influences the severity of autism. The biological environment encompasses all bacterial, viral, chemical, or physical environmental exposures and influences, directly and primarily acting on the individual physiologically. Psychosocial environmental factors indicate the social, psychological, and cultural environments that mainly act on mental functions and secondarily on physiology. Understanding of the causative part of environmental factors in the ASD etiology can possibly inform both primary banning and evidence-based interventions. Although the environment is obviously key in med interposing unnecessary negative outcomes and of overriding significance in secondary and tertiary interventions and rein forcing autistic individuals in their life. While research has examined the role of environmental factors in increasing the risk of autism, developing research balances this emphasis, reassessing the environment as a possibly etiological protective factor of ASD [27]. The environmental and genetic contributions to the etiology of ASD have broadly surveyed factors in isolation, rather than considering the role of gene environment relations via processes as changes. Epigenetic mechanisms amend gene expressions organized by factors other than DNA sequencing and are reversible. Epigenetic mechanisms, as DNA methylation, play a historic role in ASD etiology in merging environmental and genetic factors that alter neurodevelopmental processes [28-30]. A body of developing indications to various success and onset models, integrating both environmental and genetic contributions like the Trigger Threshold Target model and the three-hit concept of resilience and vulnerability, as fruitful approaches in understanding the development & etiology of the phenotype of autism [31,32].

**Environmental Factors**

Investigated biological environmental risk factors in ASD include maternal and paternal age, fetal environment (e.g. Sex steroids, maternal infections/immune activation, obesity, diabetes, hypertension, or ultrasound examinations), perinatal and obstetric events (e.g., hypoxia), medication (valproate, selective serotonin reuptake inhibitors), smoking and alcohol use, nutrition (e.g. short inter-pregnancy intervals, e.g. vitamin D, iron, zinc, and copper), vaccination, and toxic exposures (air pollution, heavy metals, pesticides, organic pollutants). Astonishingly, the role of protective factors as fatty acid and folic acid intake and examine their level at frequent times. While there are many postulated mechanisms through which these environmental factors might generate autistic behaviors and clinical variants of ASD, inflammation and immune activation, oxidative stress, hypoxia, and endocrine disruptions are likely the most pivotal in contributing to atypical neurodevelopment. Although the relevance of these factors may not be directly causal, but confounded by genetic factors, understanding is limited by the paucity of research examining gene environment interactions [27].

**Parental Age**

The advanced parental age importance is a well-proven risk factor for chromosomal aberrations, as advanced maternal age in Down syndrome. There was amassing evidence of the importance of older parental age in the neurodevelopmental and etiology of psychiatric conditions counting schizophrenia, bipolar disorder, ADHD, and
ASD substance use disorders [33,34]. While numerous hypotheses have been posed as to the biological mechanisms of an association between advanced parental age paternal and maternal age effects, and increasing likelihood of malign de novo mutations has been suggested [35]. This was most likely elucidated by mutations accumulating risk during spermatogenesis through the life span [36]. Certainly, de novo mutations linked with ASD are more overwhelmingly paternal than maternal [37]. It was found that linked autism risk in offspring of older fathers was detected with age-related DNA methylation changes in their sperm [38]. Stimulatingly, these impacts might even be intergenerational, with advanced grandparent paternal age on both father’s and mother’s side linked to ASD, proposing that parental age-related risk might accumulate over generations [22]. In neurobiology, augmented paternal age has been allied with reduced cortical thickness of the right ventral posterior cingulate cortex [39]. It has also been hypothesized that the increased risk of ASD with advancing age is elucidated by males with autism risk, in the form of a subclinical broader autism phenotype. If this is the case, the increasing risk of ASD with advancing paternal age might be elucidated by genetic tendency, rather than biological aging. However, this hypothesis was reinforced [40]. Contradicting this theory is evidence that young parental aged is linked to some neurodevelopmental disorders, for instance ADHD, a complaint often comorbid to ASD [41,42]. Parental age-related risk in ASD has been found in cohorts across multiple geographic regions; with evidence those parental age-related risks for ASD offerings independently for paternal and maternal age. There is evidence that parental age-related risk is at its maximum in offspring where both the father and mother are advanced in age, and that there is a high risk of ASD for couples with greater age differentials [43]. Also it is probable that advanced paternal age causes higher maternal age for male offspring and a higher risk for female offspring [44].

**Fetal Environment**

Numerous environmental prenatal exposures present within the immediate environment of the developing fetus such as sex hormone alterations, maternal obesity, diabetes, hypertension, infections and immune activity, and ultrasound exposure have been considered in the context of ASD etiology. While the origins of these risks might be in genetic disposition, environmental interactions involving both them other and fetus with the potential to compromise the fetal maternal placental system cannot be ignored. Plenty of these factors could be the output of the amalgamation of numerous underlying pathophysiological procedures, as the negative effects of imbalanced fetal sex hormone contact throughout critical time openings on gene transcription and expression, and subsequent neuropeptide, neurotransmitter, or immune pathways [45,46]. Obesity endures an independent risk for diabetes, being overweight, coronary heart disease, obstetric problems and several other medical situations in the offspring [47]. Also maternal obesity is presupposed to influence the cognitive functions and brain development of offspring [48]. High-fat diet and severe maternal obesity might affect offspring and fetal neurodevelopment, through processes comprising low-grade increased oxidative stress, neuroinflammation, glucose, insulin resistance & leptin signaling, dopaminergic signaling and dysregulated serotonergic, altered DNA methylation patterns and perturbations in synaptic plasticity [49,50]. All these and extra risks for neurodevelopment are augmented in the existence of co-occurring diabetes [51]. Hypertension during pregnancy contributes substantially to mortality perinatal and morbidity of both the mother and her child [48]. Hypertension may lead to sequelae of untoward utero conditions, increasing the risk of long-term vascular and potentially altering fetal development, psychiatric outcomes and cognitive in the offspring.

Increased blood pressure is the chief driver of these adverse consequences. This is mainly problematic when it is correlating with preeclampsia, which exists with significant quantities of protein in the urine and risks of low blood platelet count, red blood cell breakdown, kidney dysfunction, impaired liver function, shortness of breath, swelling, due to fluid in the lungs, and visual disturbances [52]. Infection throughout pregnancy stimulate the maternal immune system, generating cytokine signaling, passing through the placenta, and possibly producing plentiful adverse neural effects in the developing fetal brain [53].

### Vitamin D and Its Metabolism

Vitamin D is a steroid hormone that is provided through exposure to sunlight or from food sources; nevertheless, the diets consumed by most humans contain slight quantities of vitamin D, unless it is rich in fatty fish [54]. This vitamin is made from 7-dehydro-cholesterol in the skin through UVB radiation. Whether vitamin D enters the body through dermal synthesis or dietary intake, it is converted to 25-hydroxy cholecalciferol by the 25a-hydroxylase enzyme in the liver and then is activated to 1,25-dihydroxy cholecalciferol by the enzyme 1a-hydroxylase in the kidneys [35]. More than 85% of vitamin D in the circulation is strongly bound to vitamin D Binding Protein (DBP), and freeform & the fraction bound to albumin, are only the active biological forms [56]. Serum levels of 25(OH) D are the finest indicator for vitamin D status determination [57]. Regardless of sex and age, vitamin D deficiency has been reported worldwide, and according to global estimates, more than one billion people worldwide suffer from vitamin D deficiency [58]. In addition to calcium/phosphorus and bone metabolism, vitamin D plays role in regulation of immune and hormonal responses, metabolic processes, antioxidant activity, cellular differentiation & proliferation. It also has a critical role in brain development. Vitamin D affect neuroprotective and neurotrophic processes in the brain, and also potentially affects synaptic plasticity and neurotransmitters [54,59]. Vitamin D deficiency might disturb the nervous system function and possibly increases the occurrence of neurological diseases as Autism Spectrum Disorder (ASD). Vitamin D appears to have the strongest impact on the nervous system in the perinatal period. It is also associated with alterations in the mental status of adults, so that its insufficiency has been listed in neurological diseases such as depression, ASD, Multiple Sclerosis (MS), Parkinson disease, Alzheimer’s disease and Attention Deficit Hyperactivity Disorder (ADHD) [54,59].

### Vitamin D and Autism Spectrum Disorder

Several hypotheses have been proposed for the relationship between vitamin D and autism. Serum levels of vitamin D are lower than normal [57,60]. In 2012, it was found the lower serum levels of vitamin D in children with autism (mean serum levels of 15 ng/ml in children with autism compared to 30 ng/ml in healthy children), and also a significant correlation between serum vitamin D level and severity of ASD grading was listed [61]. It is not clear whether children with ASD are born with low levels of vitamin D, or limited exposure to sunshine leads to lower levels of vitamin D in ASD patients. Researchers suggested that low levels of vitamin D in children with ASD have a genetic basis [60,62]. Kocovska et al. [59] found that children with ASD have significantly lower levels of vitamin D.
compared to their siblings whom all live in an environment with low sun shine [63]. Also, Fernell et al. [64] analyzed 58 pairs of siblings, one of them with ASD and the other was healthy, and concluded that the serum levels of vitamin D at the birth time were lower in children with ASD. Schmidt et al. [65] examined the association between common vitamin D polymorphisms in charge Cohort & ASD and found that polymorphisms related to lower levels of vitamin D, were more common in children with ASD. Dissimilar opinions about the disease have proposed that oxidative stress is a possible cause of ASD. In autism, oxidative stress markers are elevated, while the level of glutathione, one of the most significant antioxidants in the body, diminished [66]. It was found that vitamin D is important in regulating the production of antioxidants as superoxide dismutase, glutathione and thioredoxin reductase [54]. So, it can exert protective effects against ASD.

**Vitamin D and ASD Mechanism**

The biological active form of vitamin D, 1,25-dihydroxyvitamin D3 [1,25(OH)2D)] binds to the Vitamin D Receptor (VDR) it then interacts with the Retinoid X Receptor (RXR) and this complex binds to the Vitamin D Response Element (VDRE) that begins to induce the expression of a number of different genes. Many of these genes act to control many different cellular control mechanisms. In addition, vitamin D controls the expression of both Nrf2 and Klotho that contribute many of the vitamin D homeostatic functions.

Figure 1: When vitamin D (1,25-dihydroxyvitamin D3 [1,25(OH)2D]) binds to the Vitamin D Receptor (VDR) it then interacts with the Retinoid X Receptor (RXR) and this complex binds to the Vitamin D Response Element (VDRE) that begins to induce the expression of a number of different genes. Many of these genes act to control many different cellular control mechanisms. In addition, vitamin D controls the expression of both Nrf2 and Klotho that contribute many of the vitamin D homeostatic functions.
It down regulates the NADPH oxidase that generates ROS while upregulating the superoxide dismutase that rapidly converts $\text{O}_2^{-}$ to $\text{H}_2\text{O}_2$. Vitamin D also up regulates expression of the glutathione peroxidase that leads to the conversion of $\text{H}_2\text{O}_2$ to water [76]. It turns out that vitamin D working together with Nrf2 and Klotho plays an essential role in maintaining the phenotypic stability of many of these cell signaling pathways and particularly the Ca$_2^+$ and redox signaling systems [77-82].

**Conclusion**

The vitamin D/Klotho/Nrf2 trio are the major custodians of such phenotypic stability and this may explain why a deficiency in vitamin D seems to affect so many of the processes that occur during development and could explain the problem of infertility and the onset of the neurodevelopmental diseases such as ADHD, autism, and schizophrenia. There is now considerable evidence to show that the epigenetic landscape is of critical importance during neural development and function. For example, a deficiency in the epigenetic factor euchromatin histone methyltransferase1 results in an alteration in brain wiring during development. The ability of vitamin D to modulate the epigenetic landscape may thus maintain the development processes via its ability to control phenotypic stability so that the right genes are activated to control each phase of development.

**References**

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