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Autism, Vitamin D and Early Brain Development

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Introduction

Humans have a number of specific skills that sets them apart from other species, such as the possibility to communicate through complex language and abstract thinking. These skills allow them to interact with others, understand the meaning of other people's actions and emotions, but also to collaborate in order to plan future events, and switch rapidly between different strategies to adapt to the environment. If somebody has autism, most of these skills are impaired, typically from an early age on and such impairments usually persist into adulthood. Autism, or Autism Spectrum Disorders (ASD) as described in the DSM-5 (Diagnostic and Statistical Manual; see dsm-5.org) are a heterogeneous group of neuropsychiatric disorders characterized by problems in social communication, as well as by the presence of restricted interests, stereotyped and repetitive behaviors. It is estimated that one in every 110 children is diagnosed with autism, making it more common than childhood cancer, juvenile diabetes and pediatric AIDS combined. The lifetime cost, if someone has autism and intellectual disability is estimated at approximately 1.45 million euro and for autism without intellectual disability is approximately 0.95 million euro. A large amount of evidence, from neuroimaging studies, genetic studies and epidemiological studies shows that the biological underpinnings of ASD are highly complex. A typical example that demonstrates this complexity is the relationship between ASD and vitamin D deficiency. To fully appreciate this, an ontogenetic perspective on vitamin D deficiency is taken and the functions of vitamin D are discussed [1], followed by a brief review on the role of vitamin D deficiency in ASD [2]. Next the genetics of autism [3] and early brain development [4] are briefly summarized, and conclusions are made.

An Ontogenetic Perspective on Vitamin D

Our genetic makeup is the result of millions of years of natural selection, resulting over the last two hundred thousand years in excellent hunting and gathering strategies, which have increased our chances for survival and procreation. Relatively recent, some ten thousand years ago, the first forms of agriculture arose, while the industrial revolution occurred only eight generations ago. It seems unlikely, that our genome has already fully adapted to the current environmental conditions and demands. Indeed, much of our genetic makeup resides in the Paleolithic era, and it has been argued that diseases such as obesity, cardiovascular diseases, metabolic syndrome, increasingly prevalent allergies, and chronic stress may be caused by a mismatch between our Paleolithic inheritance and modern lifestyles [1]. Among the large number of changes that modern lifestyles have brought, reduced time spent outdoors may be a prominent factor. One of the effects of reduced time spent outdoors is on levels of vitamin D, because cutaneous synthesis of vitamin D by exposure to UVB is the principal source of vitamin D. Evolutionary adaption to the migration of mankind to higher latitudes can clearly be seen in the gradual loss of skin pigmentation. This shows the importance of vitamin D for the survival of our species. In 2008, Cannel suggested that apparent increase in the prevalence of autism over the last 20 years corresponds with increasing medical advice to avoid the sun, advice that has probably lowered vitamin D levels and would theoretically greatly lower activated vitamin D (calcitriol) levels in developing brains [2]. Combined with the indoors postindustrial lifestyle of most people, this effect be even stronger. Before focusing on ASD and vitamin D, the different functions of vitamin D are discussed. Several forms of vitamin D exist. The two major forms are vitamin D2 or ergocalciferol, and vitamin D3 or cholecalciferol. In humans, vitamin D3 plays a major role as prohormone with both rapid and slow effects and controls the expression of about 3% of our genes. Chemically, vitamin D3 is a secosteroid that is strongly involved in the regulation of calcium levels. Synthesis of vitamin D3 in the skin is the major natural source, and only a limited amount of vitamin D3 is derived from the diet. UVB radiation from sunlight is a key factor in dermal synthesis of vitamin D3 from cholesterol. To become active, vitamin D must first be converted through hydroxylation into calcidiol, or 25-hydroxycholecalciferol. This takes place in the liver and kidneys. Next calcidiol is converted in the kidneys into calcitriol, regulating the concentration of calcium and phosphate in the bloodstream and promoting growth and remodeling of bone [3]. Recommendations on vitamin D3 serum levels vary. Controversy on the recommended levels may be related to results from studies in different ethnic populations. In contrast to older guidelines, the consensus is now that a minimum >30 ng/ml (75 nmol/l) is a reasonable cut-off. Actually, the discussion in the field is more towards even higher cut-off criteria than lower [4]. Interestingly, in studies of populations who still live in a gatherer and hunter tradition a mean circulating 25(OH) D concentration of 46 ng/ml (115 nmol/l) is reported [5]. Worldwide, vitamin D deficiency is common in children and adults [6], suggesting that lifestyle advices and supplementation strategies are important. In this respect it is important to mention that vitamin D toxicity is rare, and in healthy adults only occurs in dosages above 50.000 IU/day (note that normal supplementation is usually in dosages of 400 IU).

A Brief Overview of Vitamin D and Autism

Several studies have shown a relationship between the risk for ASD and the amount of exposure to solar UVB, maternal vitamin D levels during pregnancy and vitamin D levels in children with ASD. Also, a limited number vitamin D supplementation studies have been published. With respect to a reduced amount of exposure to solar UV-B as risk factor for developing ASD, most studies show such a relationship. In a study by Grant and Cannel, an inverse correlation between the amount of solar UVB and the prevalence of ASD was found. This study was based on a cohort of children, aged 6-17 years, living in the US [7]. It has also been found that the prevalence of ASD is higher in dark-skinned offspring of immigrant mothers to Europe, especially those coming from East Africa to Northern Europe [8]. The thought is that this may be due to the fact that dark-skinned people require a higher

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sun exposure to produce the same amount vitamin D as their white counterpart. Additionally, it has been suggested that ASD symptoms may have a seasonal improvement especially during the summer [9]. Looking at reduced maternal vitamin D levels during pregnancy as risk factor for ASD, the results are less consistent. Two studies suggested a relationship [10,11], while another study couldn't support these findings [12]. In a recently published open label prospective study high dosages of vitamin D were prescribed during pregnancy to mothers who already had children with ASD, which implied that their newborn siblings were at high risk for the recurrence of autism. The newborn siblings were followed for three years and during that time, were assessed for autism on two separate occasions: at 18 months and 36 months of age. Also the newborn infants were also prescribed vitamin D, 1000 IU/day to their third birthday. While a recurrence risk of 20% would normally be expected, only one child developed ASD. Despite the fact that caution is warranted, since there was no control group or blinding, these results are promising [13]. To date, several studies have found that vitamin D level was lower in ASD children than in healthy controls [14]. These findings were further supported in a recent meta-analysis, including 11 studies from various countries across the world, accounting for a total of 870 ASD patients and 782 healthy controls. In that study, levels of serum 25(OH) D in participants with ASD were significantly lower than controls, providing strong evidence for a putative role of lower vitamin D in ASD [14].

In 2015 the first case report was published, that showed marked improvement of autism symptoms in a 32-month-old boy with ASD and vitamin D3 deficiency [15]. Two cased controlled studies followed later that year, also suggesting a reduction of ASD symptoms after vitamin D supplementation [16,17]. However, no randomized controlled study has been published so far. Also it is unclear what the dose response rate for vitamin D supplementation is, how long supplementation should be continued, how specific the effects of vitamin D supplementation are for ASD, how age of patients may have an effect on treatment outcome etc.

Autism and Early Brain Development

The compelling data's of *in vitro, in vivo*, and animal experiments shows that vitamin D is involved in brain proliferation, differentiation, neurotrophism, neuroprotection, neurotransmission, myelination and neuroplasticity [18-20]. This seems in line with the data that is available on early brain development in ASD [21]. In general, increased or decreased fetal growth appears to be a risk factor for ASD [22]. Although information about early brain development in autism is limited, neuroanatomical studies and the associations with teratogens suggest that a deviant brain development occurs during early fetal growth [23]. A deviant brain development than appears to continue throughout life, with an increased brain growth just after birth, followed by normal or relatively slower growth in childhood. It is, however, not known whether early overgrowth occurs in all children with autism [21]. Cranial ultrasound measures in the first week after birth further show that the risk for ASD is increased in case of ventricular enlargement and parenchymal white matter lesions [24].

The early brain enlargement is thought to be related to an excess of neurons, which may have several effects. First this could result in problems of connectivity in neuronal networks. On the one hand this could be local over-connectivity, while on the other hand it could lead to long range under-connectivity [25]. Second, an excess of neurons may lead to impaired migration of neurons, typically in the first trimester of pregnancy [26]. Third, it may cause a disrupted synaptic development [21]. Interestingly, genetic findings in ASD actually hint towards disruption of genes that are involved in synaptogenesis and maintenance [27].

A Brief Summary of the Genetics of ASD

The complexity of the genetics of ASD can be understood to some extent from an evolutionary perspective. It is estimated that more than 99 percent of all species that ever lived on Earth are extinct, with only the most adaptable species remaining as survivors [28]. This ever ongoing natural selection, formulated by Charles Darwin in the mid-19th century, is the motor of evolution. A vital aspect of natural selection is genetic variation in a population, which comes from mutations in the genome, or through sexual reproduction. Mutations may occur within a gene, potentially producing a new allele that may affect the trait that the gene controls. They can also involve deletions and duplications of sections of a chromosome. Duplications are thought to be the raw material needed for new genes to evolve [29]. Further variation is caused by gene environmental interactions. For instance sunlight will activate genes that are related to pigment formation, but several mechanisms are possible. All of the mechanisms that cause genetic variation are also involved in ASD, e.g. disease may the price for the necessary genetic variation [30]. Twin and familial studies estimated the heritability of ASD to be 50%, although initially this percentage was thought to be much higher [31]. Typically, autism cannot be traced to a Mendelian (single-gene) mutation. Although several candidate genes have been located, these only have small effects on the disease risk [31]. The large number of autistic individuals with unaffected family members may result from *de novo* structural variation, e.g. deletions, duplications (or copy number variations, CNVs), translocations or inversions in genetic material during meiosis. As such, a substantial portion of autism cases is not inherited [31]. Interestingly, vitamin D may increase the rate of mutations during meiosis [32]. Gene environment interactions between multiple genes and largely unknown environmental factors further complicate matters [31].

Summary and Conclusions

This editorial is intended to provide insight in the complexity of the interplay between environmental factors, genetic risk factors and autism. Vitamin D is taken as an example, and an evolutionary perspective is taken to provide a biological framework to interpret findings of different studies. The increased prevalence of mutations and CNVs in autism may to at least some extend be related to vitamin D deficiency. Early brain development in ASD, marked by initial neuronal overgrowth and impaired white matter connectivity, me be related to vitamin D deficiency during pregnancy, vitamin D deficiency at time of birth and later through life. Supplementation with vitamin D3 may improve ASD symptoms, but many questions remain: which patients improve? What is the best form and dosage of supplementation? Are improvements of vitamin D3 supplementation followed by normalization of brain development in ASD etc.

Clearly, an important topic has been discussed, which should stimulate the field to increasingly focus on the relationship between vitamin D and ASD. Integrating data from animal studies, neuroimaging studies and randomized clinical trials, may very well provide a deeper insight and result in better treatment options for ASD patients, or even provide prevention strategies.

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