Austin Journal of Nutrition & Metabolism

Open Access

Austin Publishing Group

Commentary

How do Genes and Environment cause Autism?

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Received: April 17, 2015; **Accepted:** May 10, 2015; **Published:** May 29, 2015

Abstract

Available evidence points to synaptic formational and functional abnormalities as a possible common pathway in the etiology of autism. The pivotal role of docosahexaenoic acid (DHA) in this process could explain most known risk factors for autism. DHA supplies are limited by risk factors including male gender, certain lipid metabolism gene defects, unsupplemented baby formula and some breast milk, emigration from seashores, prematurity, multiplicity, gestational diabetes, maternal smoking, and oxidative stress. Hundreds of genes are associated with autism but none have sizable effects and most of them are either related to lipid metabolism and/or synaptic membrane issues. A significant number of autistic children may not even have a genetic influence other than gender. The gender difference may be secondary to hormonally regulated DHA production issues. Diet and/or supplementation of nutrients like DHA may be helpful in preventing ASD.

Keywords: Autism; Genes; Synapse; Diet; Docosahexaenoic acid

Abbreviations

DHA: Docosahexaenoic acid; ASD: Autism Spectrum Disorder; D6D: Delta-6-desaturase

Introduction

Autism spectrum disorder (ASD) is a neuro-developmental disorder of the brain characterized by impaired social communication along with restricted and repetitive behavior. Its prevalence has been increasing in the past few decades despite the fact that it has a large genetic etiological component. Environmental influences are not well defined or understood. Hundreds of genes have been found to be associated with it, yet little is known how those genes contribute to the etiology. The following discussion will address how a number of genes known to be associated with mental disorders including ASD can interact with environmental (mainly nutritional) factors in a logical manner that can explain most known risk factors for ASD.

Lipid metabolism genes

There are over 100 genes of known chromosomal loci involving phospholipid metabolism, and over half of them are associated with various mental disorders [1]. Many such mental disorders are represented in family histories of children with ASD, and are often experienced by ASD patients as comorbidities. Of particular interest is the desaturase gene cluster involved in the conversion of essential fatty acids into end products critical to brain function [2]. The chromosomal site containing the desaturase genes FADS1 (11q12.2-q13.1) and FADS2 (11q12.2) also is near other genes like SHANK2 (11q13.2) and DLG2 (11q14.1) which are involved in synaptic function and are associated with ASD [3]. FADS2 and FADS1 code for delta-6 desaturase (D6D) and delta-5 desaturase respectively, the rate limiting enzymes for conversion from essential fatty acids [2]. End products of conversion are the omega-6 arachidonic acid and the omega-3 docosahexaenoic acid (DHA). The latter is found in high concentrations in synaptic membranes where it enhances membrane fluidity and function [2], and can function as an intracellular neurotransmitter [1]. An enzyme involved in that intracellular release of DHA from the membrane is phospholipase A2 which is expressed by a gene linked to bipolar disorder and ASD [1].

Role of hormones

One of the greatest known risk factors for ASD is male gender. Males are known to have less DHA at birth than females [4] and have greatly reduced activity of D6D [5], likely secondary to the down-regulating effect of testosterone in contrast to the up-regulating effect of estrogen [6]. Maternal smoking is also a reported risk factor for ASD, possibly through smoking's effect of increasing testosterone levels [7]. Smoking can decrease DHA production [8].

Role of milk

DHA-supplemented formula was found to be associated with significantly reduced risk of ASD compared to DHA-unsupplemented formula [9]. Not all breast milk has the same DHA concentrations which might explain why some studies show benefit in breastfeeding for ASD [9,10] while others show potential increased risk with breastfeeding [11,12]. A recent study showed that breastfeeding could increase risk for ASD in a first-born male if the mother had psychopathology and was over 30 years old [12]. It has been shown that single nucleotide polymorphisms associated with reduced D6D activity can lower breast milk DHA content [13] even in mothers who eat more fish [14]. Older maternal age (another risk factor for ASD) is also associated with decreased D6D activity [1]. Although genotypes from mothers of ASD children did not appear to have a common variant of large effect [15], it was not studied in relationship to breastfeeding, so that potential interaction still should be investigated.

Immigration factor

Studies have shown an increased risk for ASD in children who had at least one parent migrating from one country to another [16]. A study with small numbers found not only a significant difference between ASD patients and controls with that situation, but noted that all of the ASD patient immigrant parents came from a country in which fish was a prominent part of the diet and that fish was rarely eaten where the affected child was born [12]. The highest rates of autism

Citation: Field SS. How do Genes and Environment cause Autism?. Austin J Nutr Metab. 2015;2(2): 1017.

in a study from London looking at immigrant parents occurred in those from the Caribbean islands [17] where it would be expected that many generations were used to eating a lot of fish. It was hypothesized that many generations of eating fish (rich in DHA) could select out inefficient conversion enzyme genes for generating DHA since it was being supplied by diet and that a move to a place where fish is rarely eaten could put those immigrants and their offspring at risk for DHA deficiencies at the critical time of brain development [12].

Parental age

Young paternal age has been found to be protective against ASD while older paternal age, especially over 40 years of age, is a risk factor for autism [18]. This has been largely attributed to increased mutations in sperm with age. Indeed, ASD-relevant *de novo* mutations (in germ lines) have correlated with paternal age [19]. There is some evidence that older parental age is more of a risk factor for ASD in females than in males [12] which could account for an observed shift in the male to female ratio downward with older fathers [20]. In another study, genetic defects of greater effect such as truncating mutations were more common in ASD females than in ASD males whereas high-functioning ASD patients had a similar average number of truncating mutations as unaffected siblings [3]. Likewise, the more severe autistic disorder [21] has a lower male to female ratio compared to the less severe Asperger disorder [22]. Thus ASD females tend to have a stronger genetic component to their condition while ASD males tend to have a stronger environmental component. A "protective effect" in females that has eluded investigators [3] may be their higher hormonally influenced natural levels of DHA.

Environmental risk factors

Known ASD risk factors that seem to be predominantly environmental include prematurity, low birth weight, multiplicity (e.g. twins) [23], gestational diabetes [24], maternal smoking during pregnancy [7], pollutants (including inorganic molecules and organic substances), nutritional deficiencies (particularly folic acid) [25], prenatal infections [26], oxidative stress [2] and baby formula not supplemented with DHA [9]. Since most DHA accretion in developing brains occurs in the last trimester of pregnancy and in the first few months after birth [8], being born prematurely creates a deficit of DHA for the baby. Low birth weight also points to nutritional deficiencies. In multiplicity, multiple fetal brains compete for limited maternal supplies of DHA. There has been significantly less long-chain fatty acids like DHA in fetal than in maternal plasma in gestational diabetes consistent with decreased transplacental transport [27]. Some hydrocarbons like trans-unsaturated fatty acids, air pollutants and insecticides can interfere with normal function of critical neuronal membrane components like DHA. Studies showing a correlation between autism and prenatal folic acid supplementation either did not look at simultaneous DHA (or fish oil) supplementation [28] or had data (from Table 1, eTable 1, and eTable 2) that showed a correlation between ASD prevalence and fish oil supplementation very similar to that found with folic acid supplementation [29]. The first study [28] did show a gene interaction with the supplementation, but it is also possible that one carbon transfer genes interacted with DHA as well as with folic acid [30]. Along with vitamins B-6 and B-12, folic acid can increase DHA levels in rats [31]. Intrapartum infections stimulate prostaglandins which induce cytokines which may inhibit synapse formation [2]. So for most known risk factors, limited DHA supplies or function is a plausible common denominator for their association with ASD. Add to that the decreased risk associated with increased fish consumption [32,33] and the known association between many genes involving lipid metabolism and multiple brain disorders, it is very possible that both genetic and environmental influences of lipid supplies and function could interact in the etiology of ASD.

Other genetic factors

Many genes have been found to be associated with ASD that are not directly related to lipid metabolism and some of them have been shown to interact with environmental factors [28] or other ASD-related genes through chromatin modifications and transcriptional regulation of network genes [3]. Receptor genes for the neurotransmitter, gama-aminobutyric acid [34], calcium channel genes [3] and the oxytocin (hormone) receptor gene [35] have been associated with ASD. Biological plausibility exists for all of these factors in their role in normal brain development and function, but it is also possible that deficiency of DHA, a critical synaptic membrane functional component, as well as deficiencies of other nutritional factors like iron and vitamins B-6, B-9, B-12, and D may interact with these other factors in causing autism. Many of the proposed gene mechanisms involve synapse formation and function [3], a site where DHA is most needed and functional. Despite searching thousands of ASD patients for genetic variations, no common gene defect has been found; rather hundreds of alleles have been found that could contribute to its etiology [36]. More importantly, whole genome sequencing of families who had 2 ASD children found ASD-relevant gene mutations in only 36 (42%) of the 85 families sequenced and only 14 of those families had such mutations found in both children [19]. The assumption that *all* ASD individuals have a genetic component deserves to be questioned. While there is no doubt that genes play an important role in a significant number of people with ASD, there may be another significant subset (likely to include more high-functioning cases) in which pathology comes solely from environmental influences. Greater concordance found in monozygotic than dizygotic high-functioning (Asperger) twins [22] may actually be due to shared environmental risks in the absence of genetic influences (good genes/bad environment). Of those with genetic influences, environment likely also plays an important role. The interaction of genes and environment needs to be elucidated with future research.

Future studies

More studies are needed examining genes for lipid metabolism and their association as well as potential direct role in causing ASD. Also gene activity such as that of the long-chain polyunsaturated fatty acid transport gene can be measured by messenger RNA techniques [27] which could provide useful information in addition to genomics. While it is not generally feasible to alter genomics at this time, understanding how genes and nutrient deficits contribute to disorders like ASD may lead to some prevention by compensating for genetic and environmental shortcomings with healthy diets and/or dietary supplements.

Conclusion

Most known risk factors for ASD are associated with limitations in supply of DHA for the developing brain. DHA is a common and

critical functional component of synaptic membranes in the brain. Synaptic membrane formation and function may be the most important pathogenic factor in ASD. Genetic variances associated with ASD are largely involved with lipid metabolism and synaptic membrane formation and function. Genetic and environmental influences which often interact with each other may be at least partially overcome by altering nutrient intake during and after pregnancy.

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