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Environmental Influences on Biochemistry in Autism Spectrum Disorder

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Autism Spectrum Disorder (ASD)

Autism Spectrum Disorder (ASD) diagnosis is increasing with approximately 1/68 children in the United States diagnosed with an ASD [1]. A recent survey of parents indicated that this number may be as high as 1/50 [2]. ASDs are approximately 4.5 times more prevalent in boys than girls [3]. ASDs are characterized by impaired social interactions, communication deficits and repetitive/stereotyped behavior [4,5]. Numerous susceptibility genes have been identified for ASDs, making them highly heritable disorders [6]. Many of these genes are involved in nervous system development and neurotransmitter systems [6]. Despite the numerous genetic studies performed, the causes of ASD are still poorly understood and current treatments are limited to behavioral interventions once problems have been detected [7,8]. Early detection is highly desirable to promote early behavioral interventions and more functional outcomes [9]. Although genomic studies provide clues to causes of ASD, analysis of gene products, such as proteins, should ideally be performed for comprehensive understanding of ASD [7]. Preliminary proteomic investigations have reported potential links to cholesterol dysregulation and immunological responses present in individuals with ASD [10-13]. These proteomic dysregulations could potentially be in response to certain environmental toxins, which could play a role in ASD causality [14-16]. Here we will discuss the possible genetic, proteomic and environmental contributions to this complex disorder.

Genetic Analysis of ASD

It is known that ASD is highly heritable. The risk of ASD occurring in a sibling of an autistic person is over 20 times greater than the risk for the general population and increases to 200 times greater in identical twins [17]. Numerous methods have been employed to try to determine ASD susceptibility genes which include chromosomal studies, linkage studies and gene association studies [8]. Candidate autism susceptibility genes have been identified at multiple loci, most consistently on chromosomes 2q, 7q, 15q [11-13], 17q and 16p with the most consistent positive results coming from 7q [18,19]. Although the numerous genetic studies conducted on ASD have been successful in identifying potential chromosomal abnormalities, truncations and missense mutations, the detection of the specific genetic variants responsible for ASD have been mostly elusive, likely due to the high genetic complexity and probable heterogeneity of the disorder [8]. Notably, a recent study provided the first clear link to a subtype of autism and a specific genetic mutation in the CHD8 gene [20], indicating that more progress may follow in the genetic understanding of other subtypes of ASD.

Proteomic Analysis of ASD

There are many reports of protein alterations in people with ASD which have led to investigations of the potential of protein biomarkers for use in early diagnosis. Two hypothetical dysregulated systems in individuals with ASD include cholesterol and associated molecules and the immune system. Studies have shown increased levels of two apolipoproteins, apoA1 and apoA4, responsible for lipid transport, in people with ASD compared to matched controls [13,21]. Autism is a common comorbidity for Smith-Lemli Opitz Syndrome (SLOS). SLOS is a genetic syndrome characterized by cholesterol dysregulation initiated by deficient activity of 7-dehydrocholesterol reductase [22]. The presence of autism in SLOS supports the idea that lipid associated pathways may be disrupted in ASD [17,23]. There has also been evidence of increased levels of serum paraoxanase/arylesterase 1 (PON1), which is involved in toxin metabolism and detoxification, and could help prevent oxidative stress [13]. Interestingly, PON1 is a component of high density lipoprotein (HDL) [24], further attesting to possible lipid disturbances in ASD. The presence of elevated PON1 also supports the concept that people with ASD may have increased levels of oxidative stress compared to the general population.

Environmental Influences on ASD

Along with genetic factors, environmental factors may play a role in causing ASD, due to the delicate sensitivity of the developing human brain to toxic chemicals [18,25]. Autistic children show signs of oxidative stress [26] and impaired methylation [25]. These may reflect effects of toxic exposure. When exposed to oxidative stressors temporarily, normally sulfur metabolism and epigenetic patterns are allowed to return back to normal. However, prolonged exposure to heavy metals and xenobiotics can lead to long-lasting adaptive epigenetic responses which may in turn reflect by an individual's genetic background and their risk for certain disorders, such as ASD [25].

It has been suggested that certain pesticides may be capable of producing core autism features due to their chemical compositions and toxicity. There is increasing information in this area, and further studies into the timing, dosage or mechanisms that actually induce the condition are needed [16]. Recently, results of the Childhood Autism Risks from Genetics and Environment (CHARGE) study indicated that prenatal close proximity to organophosphates was associated with a 60% increased risk for ASD. The risk increased for 3rd trimester exposure. More research into pesticides and autism is needed [15].

PON1 is a marker for organophosphate pesticide exposure [27] and as mentioned, may be elevated in individuals with ASD [13]. PON1 enzyme activity has been observed to be low in some individuals with autism [28,29] and gene mutations in PON1 are associated with autism in the United States (where there is more pesticide use) but not in Italy

[27]. This suggests that PON1 may be a marker for increased pesticide exposure in autism, but also that deficient or defective PON1 activity may predispose to ASD. It also suggests a model for gene-environment interactions in ASD causality.

Conclusions

ASD is very complex and cannot be characterized by one method alone. Proteomic, genetic and environmental links may all contribute to the disorder and are interactive, not mutually exclusive. Several studies have found proteins involved in cholesterol dysregulation and oxidative stress/immune responses to be differentially expressed in individuals with ASD. Numerous genetic investigations have been made as well in which there have been many chromosomal abnormalities along with mutations that have been detected in people with ASD. However, none of these genetic differences provide enough evidence to conclude that the disorder is genetic alone. Environmental factors, including exposure to certain pesticides and long term exposure to toxic chemicals, may increase risk for autism, in collaboration with susceptibility genes. Further investigation using multiple perspectives, will shed light on the causes of ASD.

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