

# The medical basis of autism spectrum disorder: Clues for treatment and improving the lives of the entire family

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The incidence of autism spectrum disorder (ASD) has risen at an alarming rate over the last several decades, seeming to have stabilized at a prevalence of almost 2% of children [1,2]. Although the reason for the dramatic rise continues to be debated, [3] the fact remains that a significant number of children suffer from ASD and that the disability associated with ASD spills over onto the family [4]. Recently, the combined medical, non-medical, and productivity costs has been estimated to be around \$268 billion annually, exceeding the costs of stroke and hypertension [5].

Despite the fact that decade of research has investigated the basis of ASD, the fact remains that the etiology of ASD remains poorly understood [6]. We previously pointed out that genetic-based research has long dominated the field of ASD research and the number of papers published on the genetics of ASD far outnumbers research papers on other topics [6]. This has been driven in some part by the fact that ASD appears to be highly heritable [7]. However, clinical genetic research has not supported the notion of ASD being caused by Mendelian inherited genetic defects. For example, the 2013 American College of Medical Genetic guidelines estimate that known genetic defects account for a little more than 30% of cases [8]. Most surprisingly was a recent study that demonstrated a yield of a genetic diagnosis for ASD of just 15.8% using both chromosomal microarray analysis and whole-exome sequencing [9]. Perhaps more surprising is the fact that a whole-genome sequencing study revealed that the majority of siblings with ASD demonstrate different genetic mutations, thereby suggesting that apparent familial forms of ASD are not driven by simple Mendelian inherited mutations [10]. This is consistent with studies that demonstrate a high rate of *de novo* mutations, which, for the large part, are not absolutely deleterious by themselves, but involve that mutations in genes connected through interactions of the proteins they produce [11]. This raises the question as to whether genetic mutations have arisen secondary to errors in deoxyribonucleic acid (DNA) maintenance and/or the result of DNA damage due to exposure to extrinsic and/or intrinsic stressors.

A relative large study of twins in California estimated that the environment contributes a greater percent of the risk of developing autistic disorder (58%) as compared to genetic factors (37%) [12]. A more recent study from Sweden that included twins, siblings and cousins found a slightly higher genetic contribution (~50%) and suggested that the etiology of ASD was most consistent with additive genetic and non-shared environmental effects [7s]. These studies point to the fact that an important piece of the etiology of ASD, the environment, must be included when considering the etiology of ASD. Although environmental research focusing on ASD has been increasing in recent years, [6] a recent review has pointed to the limitations in previous studies and the need for further high-quality studies [13].

Most interestingly, the review pointed to the emerging evidence of the potential interaction between genes associated with ASD and specific environmental toxicants [13]. Of course one exciting consequence of considering the environment in the etiology of ASD is the fact that the environment is a potentially modifiable risk factor that can be manipulated to reduce the incidence of ASD.

Understanding the biological mechanisms of how the environment may cause ASD is important. Several potential physiological mechanisms could translate environmental exposure to adverse biological outcomes including disruption in redox and mitochondrial metabolism as well as dysregulation of the immune system.<sup>6</sup> For example glutathione, the body's major intrinsic antioxidant, has been shown to be abnormal in cytosol and mitochondria from cell lines, [14-16] peripheral immune cells, [17] blood [18] and brain tissue [19] derived from children with ASD. Many toxicants biologically cause physiological damage through oxidative stress and these abnormalities in redox metabolism can not only cause damage to proteins, lipids and DNA, but can also cause mitochondrial dysfunction and inflammation [19,20] as well as result in alterations in the transmethylation pathway and DNA methylation [21]. As DNA methylation is essential for epigenetic control of genes, this is a pathway which can silence the gene expression without causing genetic mutations.

Best known for their essential role in the production of adenosine triphosphate (ATP) through oxidative phosphorylation, the mitochondria are also intimately involved in other essential cellular functions such as calcium buffering, redox regulation, apoptosis and inflammation. ATP produced by the mitochondria is essential for a large number of cellular systems. In general, mitochondria sit at the convergence of many of the cell's metabolic pathways where they are thought of as central to the majority of cellular metabolic functions. Thus, abnormal mitochondrial function can affect a large number of cellular systems. Abnormalities in mitochondrial function is being recognized as one of the most prevalent metabolic disorders affecting ASD [22] and many children with ASD manifest symptoms, [23] biomarkers, [22] neuroimaging findings [22] and electron transport chain defects [25] consistent with mitochondrial disease. Interestingly, only about 25% of those children with ASD and mitochondrial disease have identified genetic abnormalities to account for their mitochondrial disease, [22] suggesting that mitochondrial

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dysfunction could be secondary to other unknown cellular metabolic defects or due to damage from environmental agents. Indeed many of the same environmental agents that have been linked to autism, such as heavy metal, [13] pesticides [22] and iatrogenic medications such as acetaminophen, [26-29] have also been linked to mitochondrial dysfunction.

Still, we can think of environmental influences in a boarder sense. One of the most influential environments a child experiences is the intrauterine environment during gestation. More and more evidence is accumulating that the maternal environment is important in the development of childhood diseases, particularly ASD. One of the most compelling findings is maternal antibodies to fetal brain proteins. Mothers with particular combinations of these antibodies have offspring with ASD that may have a severe phenotype [30] and more extreme brain enlargement [30] as compared to others with ASD. Still others have provided data that points to the critical role of folate during gestation and around the time of conception in protecting from the development of ASD [32-34] and a recent rodent study suggests that folate receptor alpha autoantibodies, autoantibodies that have been found in both children with ASD and their parents, [35] may have a role disrupting folate metabolism during pregnancy [36]. Other research has pointed to the fact that a genetic polymorphism in the reduced folate carrier in mothers increases the risk of ASD in the offspring [37]. Any disruption in folate metabolism can alter methylation at a critical time during the pre-implantation stages of embryo development, resulting in devastating change to the embryo [38]. These provide examples of the importance of the maternal environment in the development of ASD and provide other examples of pathways toward interventions that may prevent the development of ASD.

Another important environmental factor is the microbiome, the trillions of microorganisms that live on our bodies. These microorganisms can have influence our immune system and influence metabolism. There is growing evidence that children with ASD have imbalances in the enteric microbiome [39]. The microbiome is being increasingly recognized as involved in the development of many childhood diseases including ASD, allergic disease and obesity [40]. Interestingly, once thought as sterile, it is being revealed that the prenatal environment has its own microbiome [41,42] suggesting that the maternal microbiome during pregnancy can affect childhood health [42]. The microbiome is established within the first two years of life [43] and preliminary data suggests that probiotics are most useful in preventing childhood disease when given during gestation or early in life [44]. As there is some evidence that microbiome disturbances could be linked to metabolic abnormalities associated with ASD, [45,46] manipulation of the microbiome could be an promising focus of ASD treatment [39].

A better understanding of the etiology of ASD can lead to the developed of treatments that target underlying pathophysiology associated with ASD as well as core and associated ASD symptoms. We recently reviewed some of the evidence for pathophysiology associated with ASD and the evidence for potential treatments [47]. It is important to recognize that considering the underlying pathophysiology of ASD is critical to developing better treatments. Failure to appreciate this fact had led to the misdirection in drug development. For example, Selective Serotonin Reuptake Inhibitors showed promising results on adults with ASD in initial studies but they could not be shown to have efficacy in the target childhood ASD population [48] his reflects differences in the pathophysiological processes believed to underlying well studied psychiatric diseases and the unique nature of ASD.

Developing treatments that target underlying pathophysiology can also steer research to developing disease modifying treatments rather than symptomatic treatments. For example, the only Food and Drug Administration (FDA) approved treatments for ASD are atypical antipsychotic medications which are indicated associated, not core, ASD symptoms. These medications do not appear to be disease modifying but rather are associated with adverse cardiometabolic effect within a short time period (*i.e.*, < 3 months) [49] and increase the risk for developing Type II Diabetes in children [50]. Subjecting children to the development of such adverse health risk factors can certain result in complicated medical management as they grow older into adulthood. Thus, there is an urgent need for drug development for children with ASD, as there currently are no FDA approved medical treatments for ASD that targets the core symptoms of ASD or corrects underlying physiological abnormalities.

Treatments that target underlying pathophysiological processes might not only alleviate ASD symptoms but may improve the lives of individuals with ASD by improving or preventing the development of comorbid disease. An interesting recent study from Sweden demonstrated substantially higher mortality rates (2.6 times higher) in individuals with ASD as compared to matched controls with lower functioning individuals with ASD having higher mortality rates than higher functioning individuals with ASD [51]. Although this was recently verified in a Danish study, [52] the Danish study primarily found evidence for neurologic and psychiatric comorbidities as a cause for higher mortality. As others have pointed out, there is a high rate of mortality associated with epilepsy in ASD, [53] providing an example of how comorbid conditions substantially impact the lives of individuals with ASD. Although the study from Sweden did indeed confirm previous studies demonstrating the substantial higher mortality rate from neurologic and psychiatric disease in ASD, especially in lower functioning individuals, it did demonstrate higher mortality rates due to other diseases including neoplasm, endocrine disease, cardiovascular, respiratory, digestive and genitourinary systems and congenital malformations [51]. Most importantly the recent study from Sweden showed the excess mortality due to suicide in higher functioning individuals with ASD, thereby highlighting potentially poorly controlled or undertreated or poorly recognized psychiatric problems in these individuals.

Thus, ASD is a complicated disorder with morbidity that spreads beyond the core behavioral symptoms which define it. Examining ASD from a biological perspective may give us insights into the treatments and prevention strategies. It is most important to consider that individuals with ASD have complicated biology that can manifest in many disease processes beyond neurologic and psychiatric disease that can cause distress and reduce quality of life and increase morbidity. Gastrointestinal [54,55] and sleep [4] disorders are two for the most obvious but other disorders such as immune, atopic and nutritional disorders can also substantially effect children with ASD [47]. This strongly argues for a multispecialty approach to evaluate and treat children with ASD in order to improve quality of life and decrease morbidity and mortality.

It is also important to appreciate that ASD is not a disease that is isolated to an individuals. Children with ASD need substantial support from their family as well as the educational and medical system. The fact that full-time behavioral therapy is recommended as the standard of care for children with ASD, demonstrates the load on the education and health systems. However, we must factor in the fact that many times at least one parent in consumed with coordinating, advocating

and caring for a child with ASD. In this sense ASD no longer affects 1 in 68 children, but 3 or more times that many individuals. We recently demonstrated the spillover effect in terms of comorbidities in sleep disturbances [4]. Improving sleep onset with melatonin [56] and behavioral modification can improve the quality of life of both the parent and the child. So, even simply interventions can have a substantial impact of the whole family.

Thus, it is time to take a more integrated approach to managing complex childhood diseases like ASD. Innovation is needed to integrate care for complex children and their families. Understanding the pathophysiology of ASD will lead to the development of more effective treatments and potentially even prevention strategies. Complete care to treat and prevent ASD will require the cooperation and coordination of multiple pediatric specialties as well as obstetricians and internal medicine specialists, potentially rivalling the current model of medical care.

### Conflict of interest

The author has no conflicts of interests to declare.

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