

Evidence for Metabolic Imbalance and Oxidative Stress

BY S. JILL JAMES, PH.D.

It is well accepted that both genetic and environmental factors interact in the development of autism. The search for these factors, however, is proving challenging, with researchers reporting little or no success in replicating findings.

The metabolic aspects of autism have received much less research attention, despite the fact that chronic biochemical imbalance often plays a primary role in the development of complex disease. The metabolism of an individual — that is, the sum of the biochemical reactions in our cells that produce energy and form the materials we need to survive — is affected by both genetic and environmental factors. As such, it gives us a window through which we can view the interactive impact of genes and the environment, and identify relevant susceptibility factors.

Two metabolic impairments of particular interest, because of their association with many neurological disorders, are:

- **Abnormal methylation.** Methylation is a chemical process in which genes are “turned on” or “turned off,” and alterations in methylation affect all bodily processes including neurologic and immune function.
- **Abnormal glutathione metabolism.** Glutathione is a crucial antioxidant — a substance needed to protect the body against the effects of heavy metals and other toxins. A deficit of glutathione leads to oxidative stress, in which rogue molecules called “free radicals” damage cells. Excessive free radical damage can lead to abnormal development and function of brain cells, gut mucosal cells and immune cells, which are often impaired in autistic children.

Despite their likely role in neurologic disorders, these processes and variations in the genes associated with them have not been evaluated in autistic children until recently. For the last several years, our Metabolic Genomics Laboratory at the Arkansas Children’s Hospital Research Institute in Little Rock has focused on autism. We are discovering that many children with autism have a severely abnormal metabolic profile, indicating significant deficits in cellular antioxidant and methylation capacity.

The best index of methylation capacity is the ratio of two substances, S-adenosylmethionine (SAM) to S-adenosylhomocysteine (SAH). (This is called the SAM/SAH ratio.) When we tested 95 autistic children and 75 age-matched control children, we found that the autistic children’s SAM/SAH ratio was about 50 percent that of unaffected control children (James et al., 2006). In addition, many autistic children exhibited a threefold reduction in the ratio of “active” glutathione (GSH) to “inactive” glutathione (GSSG). Cysteine, another substance needed for GSH synthesis, was also significantly reduced, suggesting that the building blocks for GSH synthesis may be insufficient.

These new findings are of concern because they indicate a significant decrease in cellular methylation capacity and antioxidant defense, and an increase in oxidative stress that could contribute to the pathophysiology of autism. An imbalance in intracellular levels of GSH and GSSG could provide a biochemical explanation for multiple systemic issues, such as increased frequency of infections, gastrointestinal pathology, impaired detoxification and neurologic pathology, that have been associated with both autism and glutathione depletion.

The abnormal metabolite levels in pathways of methionine and glutathione metabolism observed in autistic children may reflect subtle changes in gene products that regulate activity in these pathways. Even small variations in gene expression and enzyme activity, if expressed chronically, could have a significant impact on downstream metabolism.

It is generally accepted that complex diseases such as autism are influenced by genetic alterations at multiple and variable sites

that interact to reach a threshold of toxicity that triggers disease expression. We hypothesize that subtle alterations in gene expression may interact with environmental factors to negatively affect pathways of methionine and glutathione synthesis in autistic children. The resulting metabolic imbalance would promote chronic oxidative stress and impaired methylation capacity, and could impair normal developmental maturation of neurologic and immunologic systems.

We have used the abnormal metabolic profile of children with autism to guide us in investigating genes that may confer susceptibility to the disorder. The genetic evaluation of an entire metabolic pathway, as opposed to isolated single gene products, provides greater insights into disease pathology and can identify new options for targeted treatment strategies. To this end, our research team has evaluated multiple gene polymorphisms in 360 autistic children and 205 control subjects.

In this relatively small group of children, the results have been surprising and encouraging. Although definitive results will require a much larger study population, we found significant increases in the frequency of genetic changes (polymorphisms) that directly or indirectly affect these metabolic pathways, as well as significant gene-gene interactions (James et al., 2006). Based on these results, we hypothesize that an increased vulnerability to oxidative stress (genetic and/or

using lymphoblastoid cell lines derived from autistic children and unaffected controls. We measured the rate of intracellular free radical generation at baseline and found that the autistic cells consistently exhibited higher levels of free radicals compared to the control cells. The addition of nanomolar concentrations of thimerosal to the cells resulted in greater free radical production and induced a greater decrease in glutathione in autistic compared to control cells. Because the autistic and control cells were cultured under identical conditions, these results strongly suggest that the differences observed are due to inherent genetic or epigenetic differences. (Epigenetic changes are heritable changes in gene expression that have several causes, one of which is altered methylation.)

Because abnormal behavior is the most conspicuous manifestation of autism, most current research efforts logically focus on brain pathology. The possibility that the behavioral

environmental) and abnormal DNA methylation may contribute to the development and clinical manifestations of autism.

Taken together, our results provide strong evidence that autistic children may constitute a genetically sensitive subpopulation of children who are less able to detoxify environmental exposures. The hypothesis that a genetic component of autism could involve multiple susceptibility gene variants that interact to create a fragile, environmentally sensitive metabolic imbalance is worthy of further pursuit.

Support for a genetically based vulnerability to oxidative stress comes from recent cell culture experiments in our laboratory

manifestations of autism may derive in some cases from a genetically based metabolic derangement — one that indirectly affects the brain, immune system and gut — is a plausible but relatively unexplored hypothesis for the biologic basis of autism.

Recent evidence from our laboratory provides support for this broader view that autism involves a systemwide metabolic imbalance that could negatively affect cell function as well as prenatal and postnatal development. If proven correct, this model supports the possibility that normalizing the metabolic imbalance with targeted intervention strategies could potentially improve symptoms and arrest the progression of autism.

AUTHOR

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