

# Metabolic biomarkers of increased oxidative stress and impaired methylation capacity in children with autism<sup>1,2</sup>

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## ABSTRACT

**Background:** Autism is a complex neurodevelopmental disorder that usually presents in early childhood and that is thought to be influenced by genetic and environmental factors. Although abnormal metabolism of methionine and homocysteine has been associated with other neurologic diseases, these pathways have not been evaluated in persons with autism.

**Objective:** The purpose of this study was to evaluate plasma concentrations of metabolites in the methionine transmethylation and transsulfuration pathways in children diagnosed with autism.

**Design:** Plasma concentrations of methionine, S-adenosylmethionine (SAM), S-adenosylhomocysteine (SAH), adenosine, homocysteine, cystathionine, cysteine, and oxidized and reduced glutathione were measured in 20 children with autism and in 33 control children. On the basis of the abnormal metabolic profile, a targeted nutritional intervention trial with folinic acid, betaine, and methylcobalamin was initiated in a subset of the autistic children.

**Results:** Relative to the control children, the children with autism had significantly lower baseline plasma concentrations of methionine, SAM, homocysteine, cystathionine, cysteine, and total glutathione and significantly higher concentrations of SAH, adenosine, and oxidized glutathione. This metabolic profile is consistent with impaired capacity for methylation (significantly lower ratio of SAM to SAH) and increased oxidative stress (significantly lower redox ratio of reduced glutathione to oxidized glutathione) in children with autism. The intervention trial was effective in normalizing the metabolic imbalance in the autistic children.

**Conclusions:** An increased vulnerability to oxidative stress and a decreased capacity for methylation may contribute to the development and clinical manifestation of autism. *Am J Clin Nutr* 2004; 80:1611–7.

**KEY WORDS** Autistic disorder, biomarkers, oxidative stress, methylation, methionine, S-adenosylmethionine, S-adenosylhomocysteine, adenosine, cysteine, glutathione

## INTRODUCTION

Autism is a neurodevelopmental disability that is usually diagnosed before age 3 y and is characterized by deficits in social reciprocity and in language skills that are associated with repetitive behaviors and restricted interests (1). In addition to behavioral impairment, autistic persons have a high prevalence of gastrointestinal disease and dysbiosis (2), autoimmune disease (3), and mental retardation (4). Autism also affects many more

males than females, occurring at a ratio of 4:1. A significant role for genetics in the etiology of the autistic disorder is supported by a high concordance of autism between monozygotic twins and increased risks among siblings of affected children and of autistic symptoms associated with several heritable genetic diseases [see: Online Mendelian Inheritance in Man (OMIM) #209850 (autism; 5)]. Autism has been reported to be a comorbid condition associated with Rett syndrome (5), fragile X (6), phenylketonuria (7), adenylosuccinate lyase deficiency (8), dihydropyrimidine dehydrogenase deficiency (9), and 5'-nucleotidase hyperactivity (10); however, these genetic diseases account for <10% of cases of autism. Nonetheless, the association of autism with genetic deficits in specific enzymes suggests the possibility that the genetic component of primary autism could be expressed as a chronic metabolic imbalance that impairs normal neurodevelopment and immunologic function. The possibility that autism has a metabolic phenotype is less widely accepted but has been supported by several small studies (9, 11–14).

The current study was prompted by the serendipitous observation in a previous study that the metabolic profiles of dizygotic twins—one with Down syndrome and one with autism—were virtually identical with respect to methionine cycle and transsulfuration metabolites (15). Down syndrome, or trisomy 21, is a complex genetic and metabolic disease due to the presence of 3 copies of chromosome 21 and associated with an increased frequency of autism (16). In our previous study, children with Down syndrome had lower concentrations of metabolites in the methionine cycle and significantly lower glutathione concentrations than did control children (15).

The methionine cycle involves the regeneration of methionine via the vitamin B-12–dependent transfer of a methyl group from 5-methyltetrahydrofolate to homocysteine in the methionine synthase reaction. Methionine may then be activated by methionine adenosyltransferase to form S-adenosylmethionine (SAM), the primary methyl donor for most cellular methyltransferase reactions including the methylation of DNA, RNA, proteins, phospholipids,

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