

*Selection of Abstracts Regarding  
Various Medical Findings and  
Biomedical Treatments for Autism*

*Updated October, 2010*

This page is under construction. Please excuse errors in formatting and organization.

Kałużna-Czaplińska J, Michalska M, Rynkowski J. **Determination of tryptophan in urine of autistic and healthy children by gas chromatography/mass spectrometry.** Med Sci Monit. 2010 Oct 1;16(10):CR488-92.

Abstract

**BACKGROUND:** Tryptophan is an amino acid, which is responsible for the production of serotonin in the body. Lower levels of tryptophan may play a role in pediatric disorders. In this work the urinary level of tryptophan in autistic and healthy children was compared.

**MATERIAL/METHODS:** The samples of urine were taken from 33 autistic children (10 on a restricted diet of gluten and casein free and 23 no diet) and 21 healthy children. The level of tryptophan was determined by gas chromatography/mass spectrometry (GC/MS). In this method tryptophan was derivatized and extracted simultaneously. The method was validated.

**RESULTS:** Significantly lower relative urinary levels of tryptophan were obtained for both autistic children with a restricted diet  $1.98 \pm 1.17$   $\mu\text{g/mL}$  (mean  $\pm$ SD) and autistic children without a diet  $7.44 \pm 1.33$   $\mu\text{g/mL}$  (mean  $\pm$ SD) compared to healthy children  $14.24 \pm 2.01$   $\mu\text{g/mL}$  (mean  $\pm$ SD). The method has a limit of quantification (LOQ) of 0.15  $\mu\text{g/mL}$  and a lower limit of detection (LOD) of 0.04  $\mu\text{g/mL}$  for tryptophan in urine.

**CONCLUSIONS:** This method is precise and sensitive for the detection of low concentrations of tryptophan and can be applicable to monitoring its level in human urine. Children with autism have a higher deficiency of tryptophan than the control group of healthy children. Lower levels of tryptophan may lead to the worsening of autistic symptoms such as mild depression and increased irritability.

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Pineles SL, Avery RA, Liu GT. **Vitamin B12 optic neuropathy in autism.** *Pediatrics.* 2010 Oct;126(4):e967-70. Epub 2010 Sep 20.

#### Abstract

Dietary vitamin B12 deficiency was identified as a cause of partially reversible optic neuropathy in 3 autistic children. All of the affected children presented with gradual visual loss. Examination revealed optic atrophy, and further questioning regarding diet revealed that all 3 children had severe food selectivity and highly stereotyped diets that resulted in an almost total lack of animal products in their diets. Vitamin B12 levels were low in all 3 children. Treatment with intramuscular vitamin B12 and normalization of vitamin B12 levels resulted in improvement of visual functioning in all 3 children. These cases illustrate that food selectivity, a known complication of autism, can result in vitamin deficiency that can cause visual loss and optic atrophy. Physicians must have a high index of suspicion when evaluating children with autism and visual loss to detect this rare cause of optic atrophy.

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Yap IK, Angley M, Veselkov KA, Holmes E, Lindon JC, Nicholson JK. **Urinary Metabolic Phenotyping Differentiates Children with Autism from Their Unaffected Siblings and Age-Matched Controls.** *J Proteome Res.* 2010 May 13. [Epub ahead of print]

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#### Abstract

Autism is an early onset developmental disorder with a severe life-long impact on behavior and social functioning that has associated metabolic abnormalities. The urinary metabolic phenotypes of individuals (age range=3-9 years old) diagnosed with autism using the DSM-IV-TR criteria (n = 39; male = 35; female = 4), together with their nonautistic siblings (n = 28; male = 14; female = 14) and age-matched healthy volunteers (n = 34, male = 17; female = 17) have been characterized for the first time using <sup>1</sup>H NMR spectroscopy and pattern recognition methods. Novel findings associated with alterations in nicotinic acid metabolism within autistic individuals showing increased urinary excretion of N-methyl-2-pyridone-5-carboxamide, N-methyl nicotinic acid, and N-methyl nicotinamide indicate a perturbation in the tryptophan-nicotinic acid metabolic pathway. Multivariate statistical analysis indicated urinary patterns of the free amino acids, glutamate and taurine were significantly different between groups with the autistic children showing higher levels of urinary taurine and a lower level of urinary glutamate, indicating perturbation in sulfur and amino acid

metabolism in these children. Additionally, metabolic phenotype (metabotype) differences were observed between autistic and control children, which were associated with perturbations in the relative patterns of urinary mammalian-microbial cometabolites including dimethylamine, hippurate, and phenylacetylglutamine. These biochemical changes are consistent with some of the known abnormalities of gut microbiota found in autistic individuals and the associated gastrointestinal dysfunction and may be of value in monitoring the success of therapeutic interventions.

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Tylki-Szymanska A, Gradowska W, Sommer A, Heer A, Walter M, Reinhard C, Omran H, Sass JO, Jurecka A. **Aminoacylase 1 deficiency associated with autistic behavior.** J Inherit Metab Dis. 2010 May 18. [Epub ahead of print]

Department of Metabolic Diseases, Endocrinology and Diabetology, The Children's Memorial Health Institute, Al. Dzieci Polskich 20, 04-730, Warsaw, Poland.

#### Abstract

Aminoacylase 1 (ACY1) deficiency is a recently described inborn error of metabolism. Most of the patients reported so far have presented with rather heterogeneous neurologic symptoms. At this moment, it is not clear whether ACY1 deficiency represents a true metabolic disease with a causal relationship between the enzyme defect and the clinical phenotype or merely a biochemical abnormality. Here we present a patient identified in the course of selective screening for inborn errors of metabolism (IEM). The patient was diagnosed with autistic syndrome and admitted to the Children's Memorial Health Institute (CMHI) for metabolic evaluation. Organic acid analysis using gas chromatography-mass spectrometry (GC-MS) revealed increased urinary excretion of several N-acetylated amino acids, including the derivatives of methionine, glutamic acid, alanine, glycine, leucine, isoleucine, and valine. In Epstein-Barr virus (EBV)-transformed lymphoblasts, ACY1 activity was deficient. The mutation analysis showed a homozygous c.1057C>T transition, predicting a p.Arg353Cys substitution. Both parents were heterozygous for the mutation and had normal results in the organic acid analysis using GC-MS. This article reports the findings of an ACY1-deficient patient presenting with autistic features.

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Palmieri L, Persico AM. **Mitochondrial dysfunction in autism spectrum disorders: Cause or effect?** Biochim Biophys Acta. 2010 May 8. [Epub ahead of print]

Laboratory of Biochemistry and Molecular Biology, Department of Pharmaco-

Biology, University of Bari, Via Orabona 4, 70125, Bari, Italy; Consiglio Nazionale delle Ricerche, Institute of Biomembranes and Bioenergetics, Bari, Italy.

#### Abstract

Autism Spectrum Disorders encompass severe developmental disorders characterized by variable degrees of impairment in language, communication and social skills, as well as by repetitive and stereotypic patterns of behaviour. Substantial percentages of autistic patients display peripheral markers of mitochondrial energy metabolism dysfunction, such as (a) elevated lactate, pyruvate, and alanine levels in blood, urine and/or cerebrospinal fluid, (b) serum carnitine deficiency, and/or (c) enhanced oxidative stress. These biochemical abnormalities are accompanied by highly heterogeneous clinical presentations, which generally (but by no means always) encompass neurological and systemic symptoms relatively unusual in idiopathic autistic disorder. In some patients, these abnormalities have been successfully explained by the presence of specific mutations or rearrangements in their mitochondrial or nuclear DNA. However, in the majority of cases, abnormal energy metabolism cannot be immediately linked to specific genetic or genomic defects. Recent evidence from post-mortem studies of autistic brains points toward abnormalities in mitochondrial function as possible downstream consequences of dysreactive immunity and altered calcium ( $Ca^{2+}$ ) signalling. Copyright © 2010 Elsevier B.V. All rights reserved.

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Bradstreet JJ, Smith S, Baral M, Rossignol DA. **Biomarker-guided interventions of clinically relevant conditions associated with autism spectrum disorders and attention deficit hyperactivity disorder.** *Altern Med Rev.* 2010 Apr;15(1):15-32.

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#### Abstract

Autism spectrum disorders (ASD) and attention-deficit hyperactivity disorder (ADHD) are common and complex neurodevelopmental conditions. Diagnostic criteria for these conditions have traditionally relied solely on behavioral criteria without consideration for potential biomedical underpinnings. Newer evidence, however, reveals that ASDs are associated with: oxidative stress; decreased methylation capacity; limited production of glutathione; mitochondrial dysfunction; intestinal dysbiosis; increased toxic metal burden; immune dysregulation, characterized by a unique inflammatory bowel disease and immune activation of neuroglial cells; and ongoing brain hypoperfusion. Many of these same problems are common features in children with ADHD. These

medical conditions, whether co-morbidities or etiopathogenic, would be expected to have synergistically negative effects on the development, cognition, focus, and attention of affected children. It is likely these biological abnormalities contribute significantly to the behavioral symptoms intrinsic in these diagnoses. However, treatment for these underlying medical disorders is clinically justified, even if no clear immediate behavioral improvements are observed. This article reviews the medical literature and discusses the authors clinical experience using various biomarkers for measuring oxidative stress, methylation capacity and transsulfuration, immune function, gastrointestinal problems, and toxic metal burden. These biomarkers provide useful guides for selection, efficacy, and sufficiency of biomedical interventions. The use of these biomarkers is of great importance in young children with ADHD or individuals of any age with ASD, because typically they cannot adequately communicate regarding their symptoms.

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Herbert MR. **Contributions of the environment and environmentally vulnerable physiology to autism spectrum disorders.** *Curr Opin Neurol.* 2010 Apr;23(2):103-10.

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#### Abstract

**PURPOSE OF REVIEW:** This review presents a rationale and evidence for contributions of environmental influences and environmentally vulnerable physiology to autism spectrum disorders (ASDs). **RECENT FINDINGS:** Recent studies suggest a substantial increase in ASD prevalence above earlier Centers for Disease Control figures of one in 150, only partly explicable by data artifacts, underscoring the possibility of environmental contributors to increased prevalence. Some gene variants in ASD confer altered vulnerability to environmental stressors and exposures. De-novo mutations and advanced parental age as a risk factor for ASD also suggest a role for environment. Systemic and central nervous system pathophysiology, including oxidative stress, neuroinflammation, and mitochondrial dysfunction can be consistent with a role for environmental influence (e.g. from air pollution, organophosphates, heavy metals) in ASD, and some of the underlying biochemical disturbances (such as abnormalities in glutathione, a critical antioxidant and detoxifier) can be reversed by targeted nutritional interventions. Dietary factors and food contaminants may contribute risk. Improvement and loss of diagnosis in some with ASD suggest brain circuitry amenable to environmental modulation. **SUMMARY:** Prevalence, genetic, exposure, and pathophysiological evidence all suggest a role for environmental factors in the inception and lifelong modulation of ASD. This supports the need for seeking targets for early and ongoing medical prevention and treatment of ASD.

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Mostafa GA, El-Hadidi ES, Hewedi DH, Abdou MM. **Oxidative stress in Egyptian children with autism: relation to autoimmunity.** J Neuroimmunol. 2010 Feb 26;219(1-2):114-8. Epub 2009 Dec 24.

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#### Abstract

We are the first to study the relationship between oxidative stress (by measuring plasma F2-isoprostane, as a marker of lipid peroxidation, and glutathione peroxidase, as an antioxidant enzyme) and autoimmunity (as indicated by serum antineuronal antibodies) in a group of 44 Egyptian autistic children and 44 healthy matched-children. Our results showed that oxidative stress was found in 88.64% of autistic children. Oxidative stress, resulting from elevated plasma F2-isoprostane and/or reduced glutathione peroxidase, had significant risk for antineuronal positivity, which was found in 54.5% of autistic children, (odds ratio: 12.38 and 6.43, respectively, confidence interval: 1.37-112.10 and 1.21-34.19, respectively). Conclusions: the strong association between oxidative stress and autoimmunity in autistic children may indicate the possible role of oxidative stress, through induction of autoimmunity, in some autistic patients. Therefore, studies considering the role of antioxidants and immunotherapy in amelioration of autistic manifestations are recommended. Copyright 2009 Elsevier B.V. All rights reserved.

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El-Ansary A, Al-Daihan S, Al-Dbass A, Al-Ayadhi L. **Measurement of selected ions related to oxidative stress and energy metabolism in Saudi autistic children.** Clin Biochem. 2010 Jan;43(1-2):63-70.

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#### Abstract

**OBJECTIVES:** Autism is a developmental disorder characterized by social and emotional deficits, language impairments and stereotyped behaviors that manifest in early postnatal life. This study aims to clarify the role of selected ions related to energy metabolism as a consequence of oxidative stress in the deterioration accompanied autism. **MATERIALS AND METHODS:** Malonaldehyde as measure of lipid peroxidation, Na(+)/K(+) ion pump (ATPase), together with the concentrations of Na(+), K(+), Mg(2+), Ca(2+) and Pb(2+) were determined in plasma of 30 Saudi autistic patients and compared to 30 age-matching control samples. **RESULTS:** The obtained data recorded

that Saudi autistic patients have a remarkable higher activities of Na(+)/K(+) ATPase and high levels of lipid peroxidation compared to control. In addition, they have significantly elevated levels of K(+) and Pb(2+) while Ca(2+) recorded a significantly lower level compared to age-matching control subjects. On the other hand both Mg(2+) and Na(+) were non-significantly changed in autistic patients. CONCLUSION: Alteration of the selected measured ions confirms that oxidative stress and defective mitochondrial energy production could represent the primary causative factor in the pathogenesis of autism. Copyright 2009 The Canadian Society of Clinical Chemists. Published by Elsevier Inc. All rights reserved.

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Youn SI, Jin SH, Kim SH, Lim S. **Porphyria in Korean children with autism: correlation with oxidative stress.** J Toxicol Environ Health A. 2010 Jan;73(10):701-10.

Department of Basic Eastern Medical Science, Graduate School, KyungHee University, Seoul, Republic of Korea.

#### Abstract

Autism spectrum disorder (ASD) is a neurodevelopmental disorder believed to be associated with heavy metal exposure, especially mercury (Hg), and is characterized by disturbances in metal elimination. Various studies correlated elevated heavy metal body burden with ASD diagnoses as evidenced by increased urinary porphyrin levels in patients. Urinary porphyrins were also determined in Korean patients diagnosed with ASD (n = 65) who visited AK Eastern Medicinal Clinic in Kangnam-gu, Seoul, from June 2007 to September 2008, compared to controls (n = 9) residing in the same area, by means of Metamatrix (CLIA-approved) laboratory testing. Further, urinary organic acids as indicators of hepatic detoxification/oxidative stress were also analyzed among patients diagnosed with ASD. Significant increases were found in patients diagnosed with ASD for porphyrins, pentacarboxyporphyrin, precoproporphyrin, coproporphyrins, and total porphyrins. Significant correlations were observed between hepatic detoxification/oxidative stress markers and urinary porphyrins. In agreement with published data, the present results demonstrated that measurement of porphyrins serves as a reliable tool for diagnosis of heavy metal involvement in ASD.

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Kinney DK, Barch DH, Chayka B, Napoleon S, Munir KM. **Environmental risk factors for autism: do they help cause de novo genetic mutations that contribute to the disorder?** Med Hypotheses. 2010 Jan;74(1):102-6.

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#### Abstract

Recent research has discovered that a number of genetic risk factors for autism are de novo mutations. Advanced parental age at the time of conception is associated with increased risk for both autism and de novo mutations. We investigated the hypothesis that other environmental factors associated with increased risk for autism might also be mutagenic and contribute to autism by causing de novo mutations. A survey of the research literature identified 9 environmental factors for which increased pre-conceptual exposure appears to be associated with increased risk for autism. Five of these factors--mercury, cadmium, nickel, trichloroethylene, and vinyl chloride--are established mutagens. Another four--including residence in regions that are urbanized, located at higher latitudes, or experience high levels of precipitation--are associated with decreased sun exposure and increased risk for vitamin D deficiency. Vitamin D plays important roles in repairing DNA damage and protecting against oxidative stress--a key cause of DNA damage. Factors associated with vitamin D deficiency will thus contribute to higher mutation rates and impaired repair of DNA. We note how de novo mutations may also help explain why the concordance rate for autism is so markedly higher in monozygotic than dizygotic twins. De novo mutations may also explain in part why the prevalence of autism is so remarkably high, given the evidence for a strong role of genetic factors and the low fertility of individuals with autism--and resultant selection pressure against autism susceptibility genes. These several lines of evidence provide support for the hypothesis, and warrant new research approaches--which we suggest--to address limitations in existing studies. The hypothesis has implications for understanding possible etiologic roles of de novo mutations in autism, and it suggests possible approaches to primary prevention of the disorder, such as addressing widespread vitamin D deficiency and exposure to known mutagens.

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Rossignol, DA. **Novel and emerging treatments for autism spectrum disorders: a systematic review.** Ann Clin Psychiatry. 2009 Oct-Dec;21(4):213-36.

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#### Abstract

**BACKGROUND:** Currently, only one medication (risperidone) is FDA-approved for the treatment of autism spectrum disorders (ASD). Perhaps for this reason, the use of novel, unconventional, and off-label treatments for ASD is common, with up to 74% of children with ASD using these treatments; however, treating physicians are often unaware of this usage. **METHODS:** A systematic literature

search of electronic scientific databases was performed to identify studies of novel and emerging treatments for ASD, including nutritional supplements, diets, medications, and nonbiological treatments. A grade of recommendation ("Grade") was then assigned to each treatment using a validated evidence-based guideline as outlined in this review: A: Supported by at least 2 prospective randomized controlled trials (RCTs) or 1 systematic review. B: Supported by at least 1 prospective RCT or 2 nonrandomized controlled trials. C: Supported by at least 1 nonrandomized controlled trial or 2 case series. D: Troublingly inconsistent or inconclusive studies or studies reporting no improvements. Potential adverse effects for each treatment were also reviewed. RESULTS: Grade A treatments for ASD include melatonin, acetylcholinesterase inhibitors, naltrexone, and music therapy. Grade B treatments include carnitine, tetrahydrobiopterin, vitamin C, alpha-2 adrenergic agonists, hyperbaric oxygen treatment, immunomodulation and anti-inflammatory treatments, oxytocin, and vision therapy. Grade C treatments for ASD include carnosine, multivitamin/mineral complex, piracetam, polyunsaturated fatty acids, vitamin B6/magnesium, elimination diets, chelation, cyproheptadine, famotidine, glutamate antagonists, acupuncture, auditory integration training, massage, and neurofeedback. CONCLUSIONS: The reviewed treatments for ASD are commonly used, and some are supported by prospective RCTs. Promising treatments include melatonin, antioxidants, acetylcholinesterase inhibitors, naltrexone, and music therapy. All of the reviewed treatments are currently considered off-label for ASD (ie, not FDA-approved) and some have adverse effects. Further studies exploring these treatments are needed. Physicians treating children with an ASD should make it standard practice to inquire about each child's possible use of these types of treatments.

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Dufault R, Schnoll R, Lukiw WJ, Leblanc B, Cornett C, Patrick L, Wallinga D, Gilbert SG, Crider R. **Mercury exposure, nutritional deficiencies and metabolic disruptions may affect learning in children.** Behav Brain Funct. 2009 Oct 27;5:44.

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#### Abstract

Among dietary factors, learning and behavior are influenced not only by nutrients, but also by exposure to toxic food contaminants such as mercury that can disrupt metabolic processes and alter neuronal plasticity. Neurons lacking in plasticity are a factor in neurodevelopmental disorders such as autism and mental retardation. Essential nutrients help maintain normal neuronal plasticity. Nutritional deficiencies, including deficiencies in the long chain polyunsaturated fatty acids eicosapentaenoic acid and docosahexaenoic acid, the amino acid methionine, and the trace minerals zinc and selenium, have

been shown to influence neuronal function and produce defects in neuronal plasticity, as well as impact behavior in children with attention deficit hyperactivity disorder. Nutritional deficiencies and mercury exposure have been shown to alter neuronal function and increase oxidative stress among children with autism. These dietary factors may be directly related to the development of behavior disorders and learning disabilities. Mercury, either individually or in concert with other factors, may be harmful if ingested in above average amounts or by sensitive individuals. High fructose corn syrup has been shown to contain trace amounts of mercury as a result of some manufacturing processes, and its consumption can also lead to zinc loss. Consumption of certain artificial food color additives has also been shown to lead to zinc deficiency. Dietary zinc is essential for maintaining the metabolic processes required for mercury elimination. Since high fructose corn syrup and artificial food color additives are common ingredients in many foodstuffs, their consumption should be considered in those individuals with nutritional deficits such as zinc deficiency or who are allergic or sensitive to the effects of mercury or unable to effectively metabolize and eliminate it from the body.

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Sajdel-Sulkowska EM, Xu M, Koibuchi N. **Increase in cerebellar neurotrophin-3 and oxidative stress markers in autism.** *Cerebellum*. 2009 Sep;8(3):366-72.

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#### Abstract

Autism is a neurodevelopmental disorder characterized by social and language deficits, ritualistic-repetitive behaviors and disturbance in motor functions. Data of imaging, head circumference studies, and Purkinje cell analysis suggest impaired brain growth and development. Both genetic predisposition and environmental triggers have been implicated in the etiology of autism, but the underlying cause remains unknown. Recently, we have reported an increase in 3-nitrotyrosine (3-NT), a marker of oxidative stress damage to proteins in autistic cerebella. In the present study, we further explored oxidative damage in the autistic cerebellum by measuring 8-hydroxydeoxyguanosine (8-OH-dG), a marker of DNA modification, in a subset of cases analyzed for 3-NT. We also explored the hypothesis that oxidative damage in autism is associated with altered expression of brain neurotrophins critical for normal brain growth and differentiation. The content of 8-OH-dG in cerebellar DNA isolated by the proteinase K method was measured using an enzyme-linked immunosorbent assay (ELISA); neurotrophin-3 (NT-3) levels in cerebellar homogenates were measured using NT-3 ELISA. Cerebellar 8-OH-dG showed trend towards higher levels with the increase of 63.4% observed in autism. Analysis of cerebellar NT-3 showed a significant ( $p = 0.034$ ) increase (40.3%) in autism. Furthermore, there was a significant positive correlation between cerebellar

NT-3 and 3-NT ( $r = 0.83$ ;  $p = 0.0408$ ). These data provide the first quantitative measure of brain NT-3 and show its increase in the autistic brain. Altered levels of brain NT-3 are likely to contribute to autistic pathology not only by affecting brain axonal targeting and synapse formation but also by further exacerbating oxidative stress and possibly contributing to Purkinje cell abnormalities.

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Al-Mosalem OA, El-Ansary A, Attas O, Al-Ayadhi L. **Metabolic biomarkers related to energy metabolism in Saudi autistic children.** Clin Biochem. 2009 Jul;42(10-11):949-57. Epub 2009 Apr 17.

Biochemistry Department, Science College, King Saud University, P.O Box 22452, Zip code 11495, Riyadh, Saudi Arabia.

#### Abstract

**OBJECTIVES:** Energy metabolism is usually manipulated in many neurodegenerative diseases. Autism is considered a definable systemic disorder resulting in a number of diverse factors that may affect the brain development and functions both pre and post natal. The increased prevalence of autism will have enormous future public implications and has stimulated intense research into potential etiologic factors. This study aims to establish a connection between autism and the deterioration accompanied it, especially in the brain cognitive areas through a postulation of energy manipulation.

**MATERIALS AND METHODS:** The biochemical changes in activities of enzymes and pathways that participate in the production of ATP as the most important high-energy compound needed by the human brain were measured in Saudi autistic children. Na(+)/K(+)ATPase, ectonucleotidases (NTPDases) (ADPase and ATPase) and creatine kinase (CK), were assessed in plasma of 30 Saudi autistic patients and compared to 30 age-matching control samples. In addition, adenosine mono, di and trinucleotides (ATP, ADP, and AMP) were measured calorimetrically in the red blood cells of both groups and the adenylate energy charge (AEC) was calculated. Moreover, lactate concentration in plasma of both groups was monitored.

**RESULTS:** The obtained data recorded 148.77% and 72.35% higher activities of Na(+)/K(+)ATPase and CK respectively in autistic patients which prove the impairment of energy metabolism in these children compared to age and sex matching healthy controls. While ADPase was significantly higher in autistic patients, ATPase were non-significantly elevated compared to control. In spite of the significant increase of Na(+)/K(+)ATPase activity in autistic patients, there was no significant difference in the levels of ATP, ADP, and AMP in both groups and the calculated AEC values were  $0.814 \pm 0.094$  and  $0.806 \pm 0.081$  for autistic and control groups respectively. The unchanged AEC value in autistic patients was easily correlated with the induced activity of CK and ADPase as two enzymes playing a critical role in the stabilization of AEC. Lactate as an important energy

metabolite for the brain was significantly higher in autistic patients compared to control showing about 40% increase. CONCLUSION: The present study confirmed the impairment of energy metabolism in Saudi autistic patients which could be correlated to the oxidative stress previously recorded in the same investigated samples. The identification of biochemical markers related to autism would be advantageous for earlier clinical diagnosis and intervention.

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Desjardins S, Doyen C, Contejean Y, Kaye K, Paubel P. **[Treatment of a serious autistic disorder in a child with Naltrexone in an oral suspension form]** [Article in French]. *Encephale*. 2009 Apr;35(2):168-72.

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#### Abstract

**CLINICAL BACKGROUND:** Autism is a developmental disorder that is usually diagnosed in early childhood. According to ICD-10 criteria, autism can be characterized by delays in language skills, by impaired social interaction, verbal or non-verbal communication and by repetitive, stereotyped or severely restricted activities and interests. The causes of autism are not yet elucidated, but both genetics and environment seem to play a role in 10 to 25% of autism cases. Several biochemical abnormalities, such as impairment of serotonergic, catecholnergic, dopaminergic, and opioid systems have been reported. Autism therapies are designed to treat symptoms, and medication can be associated with psychoeducational and environmental interventions. Generally, the medications that are currently used are not intended for autism, and must be used with caution and selected according to the type and intensity of symptoms. The most common medication consists of psychotropic therapies by administration of dopaminergic and/or serotonergic receptor antagonists (haloperidol, risperidone, clomipramine). Several drugs, such as anxiolytics (buspirone), mood stabilisers (lithium, sodium valproate), vitamins (vitamins B6, B12) or opioid antagonists (naltrexone) can be prescribed, in second intention, in cases of severe behavioural disorders. The prescription of opioid antagonists is based on the possible implication of an opioid system disorder observed in some cases. Nevertheless, several clinical studies reveal its variable effectiveness. Naltrexone is a competitive antagonist of opioid receptors OPRM1, OPRD1 and OPRK1. In France, this drug is prescribed for treating opioid and alcohol dependence. Moreover, several studies describe naltrexone as a possible treatment of autistic children in cases of developmental disorder and hyperactivity. **CLINICAL CASE:** In the Child and Adolescent Psychopathology Department of Sainte-Anne's Hospital, autistic children benefit from a multidisciplinary treatment program that sometimes includes the administration of psychotropic medication. One of these children

presented with a severe autistic disorder according to the Childhood Autism Rating Scale (CARS). Considering ICD-10 criteria, he benefited from a multidisciplinary program, associating cognitive psychotherapy, psychomotor rehabilitation, speech therapy and educational intervention. However, persistent sleep disorder and motor instability led to successive prescriptions of several different psychotropic drugs. Initial treatment by thioridazine (10mg per day) followed by propericiazine (2.5mg per day) improved sleep, but was not efficient in reducing self-mutilating behaviour. A new treatment by risperidone (from 0.5mg to 1.5mg per day) was therefore chosen; however it lost its efficacy after five months. Finally, an anxiolytic (cyamemazine) and a thymoregulator (sodium valproate) were successively tried without yielding any clinical improvement. Owing to the persistence of communication difficulties, major instability, self-mutilating behaviour and heteroaggressiveness, treatment with naltrexone was subsequently chosen with parental consent. In France, naltrexone hydrochloride is only available in tablet form (Nalorex 50mg and Revia 50mg), which is not adapted to children at the efficient dose. Consequently, an oral suspension form marketed in Spain (Antaxone 50mg) was imported, having obtained the Afssaps' (the French drug administration) authorisation for its temporary use. The Connors and Nisonger scales were used as outcome measures of behavioural symptom change. The Connors scale is used to assess attention deficit and hyperactivity, whereas the Nisonger scale analyses social skills and behaviour disorders in children and adolescents with mental retardation. The onset of treatment, at a dose of 1mg/kg/day, led to a transitory increase in negative behaviour. However, a dose of 0.75mg/kg per day subsequently led to significant improvements, as shown by outcome measurements. Self-mutilating behaviour disappeared completely. Certain side effects were observed, namely transitory sedation at the beginning of treatment and moderate constipation. **CONCLUSION: This clinical case confirms that treatment of a serious autistic disorder in children using Naltrexone in oral suspension form is a potentially interesting therapeutic alternative for treating behavioural symptoms resistant to classical drug therapy.**

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Brown N, Panksepp J. **Low-dose naltrexone for disease prevention and quality of life.** Med Hypotheses. 2009 Mar;72(3):333-7.

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#### Abstract

The use of low-dose naltrexone (LDN) for the treatment and prophylaxis of various bodily disorders is discussed. Accumulating evidence suggests that LDN can promote health supporting immune-modulation which may reduce various oncogenic and inflammatory autoimmune processes. Since LDN can

upregulate endogenous opioid activity, it may also have a role in promoting stress resilience, exercise, social bonding, and emotional well-being, as well as amelioration of psychiatric problems such as autism and depression. It is proposed that LDN can be used effectively as a buffer for a large variety of bodily and mental ailments through its ability to beneficially modulate both the immune system and the brain neurochemistries that regulate positive affect.

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James SJ, Melnyk S, Fuchs G, Reid T, Jernigan S, Pavliv O, Hubanks A, Gaylor DW. **Efficacy of methylcobalamin and folinic acid treatment on glutathione redox status in children with autism.** Am J Clin Nutr. 2009 Jan;89(1):425-30.

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#### Abstract

**BACKGROUND:** Metabolic abnormalities and targeted treatment trials have been reported for several neurobehavioral disorders but are relatively understudied in autism. **OBJECTIVE:** The objective of this study was to determine whether or not treatment with the metabolic precursors, methylcobalamin and folinic acid, would improve plasma concentrations of transmethylation/transsulfuration metabolites and glutathione redox status in autistic children. **DESIGN:** In an open-label trial, 40 autistic children were treated with 75 microg/kg methylcobalamin (2 times/wk) and 400 microg folinic acid (2 times/d) for 3 mo. Metabolites in the transmethylation/transsulfuration pathway were measured before and after treatment and compared with values measured in age-matched control children. **RESULTS:** The results indicated that pretreatment metabolite concentrations in autistic children were significantly different from values in the control children. The 3-mo intervention resulted in significant increases in cysteine, cysteinylglycine, and glutathione concentrations ( $P < 0.001$ ). The oxidized disulfide form of glutathione was decreased and the glutathione redox ratio increased after treatment ( $P < 0.008$ ). Although mean metabolite concentrations were improved significantly after intervention, they remained below those in unaffected control children. **CONCLUSION:** The significant improvements observed in transmethylation metabolites and glutathione redox status after treatment suggest that targeted nutritional intervention with methylcobalamin and folinic acid may be of clinical benefit in some children who have autism. This trial was registered at (clinicaltrials.gov) as NCT00692315.

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Krajcovicova-Kudlackova M, Valachovicova M, Mislanova C, Hudecova Z, Sustrova M, Ostatnikova D. **Plasma concentrations of selected antioxidants in**

**autistic children and adolescents.** Bratisl Lek Listy. 2009;110(4):247-50.

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#### Abstract

Few studies have demonstrated an increased vulnerability to oxidative stress in autism. The results of previous studies have shown that endogenous antioxidant defence is insufficient, indicating that exogenous antioxidant could play a crucial role for oxidative stress prevention in autism. Plasma concentrations of vitamins C, E, A, carotenoids beta-carotene and lycopene were measured in 51 subjects with autistic spectrum disorders aged 5-18 years (27 children aged 5-10 years, 24 subjects aged 11-18 years). Older autistic group was compared with a group of healthy Slovak subjects aged 11-18 years. Older autistic subjects vs. healthy control showed significantly higher vitamin C and beta-carotene plasma values with 92% and 71% vs 54% and 13% of optimal over-threshold values, respectively. This indicates a reduced risk of free radical disease. In younger vs. older autistic group the similarly high plasma vitamin concentrations were recorded. Favourable values of these vitamins suggested that consumption of fruit and vegetables in autistic subjects is optimal. Autistic average vitamin E and A plasma concentrations (non-significantly changed in comparison to control group) were below-threshold with low percentage of over-threshold values. Insufficient vitamin E and A plasma values indicate lower consumption of food rich in vitamins A and E (e.g. whole-grain products, plant oils, oil seeds, nuts, fat spreads and dairy products). Autistic average lycopene concentration is lower in comparison to published non-Slovak data. Conclusions of this pilot study suggest that plasma concentrations of exogenous antioxidants, vitamins E and A, and lycopene in autistic subjects are insufficient (Tab. 1, Ref. 30). Full Text (Free, PDF) [www.bmj.sk](http://www.bmj.sk).

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James SJ, Melnyk S, Jernigan S, Hubanks A, Rose S, Gaylor DW. **Abnormal Transmethylation/transsulfuration Metabolism and DNA Hypomethylation Among Parents of Children with Autism.** J Autism Dev Disord. 2008 Nov;38(10):1976.

Department of Pediatrics, University of Arkansas for Medical Sciences, Little Rock, AR, 72202, USA, jamesjill@uams.edu. No abstract available.

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Campbell, Daniel B. et al. **"Distinct Genetic Risk Based on Association of MET in Families With Co-occurring Autism and Gastrointestinal Conditions."** *Pediatrics*, 10.1542/peds.2008-0819.

Sousa I, Clark TG, Toma C, Kobayashi K, Choma M, Holt R, Sykes NH, Lamb JA, Bailey AJ, Battaglia A, Maestrini E, Monaco AP. **"MET and autism susceptibility: family and case-control studies."** *Eur J Hum Genet.* 2008 Nov 12.

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Chungpaibulpatana J, Sumpatanarax T, Thadaku N, Chantharatreeerat C, Konkaew M, Aroonlimsawas M. **Hyperbaric oxygen therapy in Thai autistic children.** *J Med Assoc Thai.* 2008 Aug;91(8):1232-8.

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#### Abstract

**BACKGROUND:** Autism is a developmental and behavioral pattern, the triad of impairments, 1. social interaction, 2. social communication, 3. imagination. Their memories are seemingly in picture or photo records. Difficulties in the treatment, management, and handling of autistic children are the main problems. Hyperbaric oxygen therapy (HBOT) is a modern treatment in Thailand for nitrogen imbalance (Decompression sickness syndrome or Caisson disease). HBOT can increase plasma oxygen to the tissues including the brain. **OBJECTIVE:** To determine whether Hyperbaric Oxygen Therapy is safe to use in children with autism, and has a statistically significant effect on autistic symptoms. This is the first study in Thailand. **MATERIAL AND METHOD:** Thai Autistic children (n = 7) received HBOT (1.3 atm., 10 sessions) treatment. Assessment was done before and after treatment in five domains: Social development, Fine motor and Eye-hand coordination, Language development, Gross motor development, Self-help skills. **RESULTS:** Improvement was shown in five domains with a significant level. Seventy-five percent of children shown improvement while 25% did not seem to respond to the treatment. **CONCLUSION:** HBOT is a new treatment for Thai autistic children. Many scientific studies recently have shown that HBOT could be an effective treatment for autistic children. It could improve the major autistic symptoms.

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Tsaluchidu S, Cocchi M, Tonello L, Puri BK. **Fatty acids and oxidative stress in psychiatric disorders.** *BMC Psychiatry.* 2008 Apr 17;8 Suppl 1:S5.

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#### Abstract

**BACKGROUND:** The aim of this study was to determine whether there is published evidence for increased oxidative stress in neuropsychiatric disorders. **METHODS:** A PubMed search was carried out using the MeSH

search term 'oxidative stress' in conjunction with each of the DSM-IV-TR diagnostic categories of the American Psychiatric Association in order to identify potential studies. RESULTS: There was published evidence of increased oxidative stress in the following DSM-IV-TR diagnostic categories: mental retardation; autistic disorder; Rett's disorder; attention-deficit hyperactivity disorder; delirium; dementia; amnesic disorders; alcohol-related disorders; amphetamine (or amphetamine-like)-related disorders; hallucinogen-related disorders; nicotine-related disorders; opioid-related disorders; schizophrenia and other psychotic disorders; mood disorders; anxiety disorders; sexual dysfunctions; eating disorders; and sleep disorders. CONCLUSION: Most psychiatric disorders are associated with increased oxidative stress. Patients suffering from that subgroup of these psychiatric disorders in which there is increased lipid peroxidation might therefore benefit from fatty acid supplementation (preferably with the inclusion of an antioxidant-rich diet) while patients suffering from all these psychiatric disorders might benefit from a change to a whole-food plant-based diet devoid of refined carbohydrate products.

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McCann D, Barrett A, Cooper A, Crumpler D, Dalen L, Grimshaw K, Kitchin E, Lok K, Porteous L, Prince E, Sonuga-Barke E, Warner JO, Stevenson J. **“Food additives and hyperactive behaviour in 3-year-old and 8/9-year-old children in the community: a randomised, double-blinded, placebo-controlled trial.”** *Lancet*. 2007 Nov 3;370(9598):1560-7.

School of Psychology, Department of Child Health, University of Southampton, Southampton, UK.

#### Abstract

**BACKGROUND:** We undertook a randomised, double-blinded, placebo-controlled, crossover trial to test whether intake of artificial food colour and additives (AFCA) affected childhood behaviour. **METHODS:** 153 3-year-old and 144 8/9-year-old children were included in the study. The challenge drink contained sodium benzoate and one of two AFCA mixes (A or B) or a placebo mix. The main outcome measure was a global hyperactivity aggregate (GHA), based on aggregated z-scores of observed behaviours and ratings by teachers and parents, plus, for 8/9-year-old children, a computerised test of attention. This clinical trial is registered with Current Controlled Trials (registration number ISRCTN74481308). Analysis was per protocol. **FINDINGS:** 16 3-year-old children and 14 8/9-year-old children did not complete the study, for reasons unrelated to childhood behaviour. Mix A had a significantly adverse effect compared with placebo in GHA for all 3-year-old children (effect size 0.20 [95% CI 0.01-0.39],  $p=0.044$ ) but not mix B versus placebo. This result persisted when analysis was restricted to 3-year-old children who consumed more than 85% of juice and had no missing data (0.32 [0.05-0.60],  $p=0.02$ ).

8/9-year-old children showed a significantly adverse effect when given mix A (0.12 [0.02-0.23],  $p=0.023$ ) or mix B (0.17 [0.07-0.28],  $p=0.001$ ) when analysis was restricted to those children consuming at least 85% of drinks with no missing data. INTERPRETATION: Artificial colours or a sodium benzoate preservative (or both) in the diet result in increased hyperactivity in 3-year-old and 8/9-year-old children in the general population.

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MacCabe DF, et al. **“Neurobiological effects of intraventricular propionic acid in rats: possible role of short chain fatty acids on the pathogenesis and characteristics of autism spectrum disorders.”** *Behav Brain Res.* 2007 Jan 10;176(1):149-69.

The Kilee Patchell-Evans Autism Research Group, Department of Psychology, Division of Developmental Disabilities, University of Western Ontario, Social Science Centre, London, Canada. [dmacfabe@uwo.ca](mailto:dmacfabe@uwo.ca)

#### Abstract

Clinical observations suggest that certain gut and dietary factors may transiently worsen symptoms in autism spectrum disorders (ASD), epilepsy and some inheritable metabolic disorders. Propionic acid (PPA) is a short chain fatty acid and an important intermediate of cellular metabolism. PPA is also a by-product of a subpopulation of human gut enterobacteria and is a common food preservative. We examined the behavioural, electrophysiological, neuropathological, and biochemical effects of treatment with PPA and related compounds in adult rats. Intraventricular infusions of PPA produced reversible repetitive dystonic behaviours, hyperactivity, turning behaviour, retropulsion, caudate spiking, and the progressive development of limbic kindled seizures, suggesting that this compound has central effects. Biochemical analyses of brain homogenates from PPA treated rats showed an increase in oxidative stress markers (e.g., lipid peroxidation and protein carbonylation) and glutathione S-transferase activity coupled with a decrease in glutathione and glutathione peroxidase activity. Neurohistological examinations of hippocampus and adjacent white matter (external capsule) of PPA treated rats revealed increased reactive astrogliosis (GFAP immunoreactivity) and activated microglia (CD68 immunoreactivity) suggestive of a neuroinflammatory process. This was coupled with a lack of cytotoxicity (cell counts, cleaved caspase 3' immunoreactivity), and an increase in phosphorylated CREB immunoreactivity. We propose that some types of autism may be partial forms of genetically inherited or acquired disorders involving altered PPA metabolism. Thus, intraventricular administration of PPA in rats may provide a means to model some aspects of human ASD in rats.

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*Summary of Biomedical Treatments for Autism* by James B. Adams, Ph.D., April 2007, published online at <http://autism.asu.edu>.

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James SJ, et al. "**Metabolic endophenotype and related genotypes are associated with oxidative stress in children with autism.**" *Am J Med Genet B Neuropsychiatr Genet*. 2006 Dec 5;141(8):947-56.

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#### Abstract

Autism is a behaviorally defined neurodevelopmental disorder usually diagnosed in early childhood that is characterized by impairment in reciprocal communication and speech, repetitive behaviors, and social withdrawal. Although both genetic and environmental factors are thought to be involved, none have been reproducibly identified. The metabolic phenotype of an individual reflects the influence of endogenous and exogenous factors on genotype. As such, it provides a window through which the interactive impact of genes and environment may be viewed and relevant susceptibility factors identified. Although abnormal methionine metabolism has been associated with other neurologic disorders, these pathways and related polymorphisms have not been evaluated in autistic children. Plasma levels of metabolites in methionine transmethylation and transsulfuration pathways were measured in 80 autistic and 73 control children. In addition, common polymorphic variants known to modulate these metabolic pathways were evaluated in 360 autistic children and 205 controls. The metabolic results indicated that plasma methionine and the ratio of S-adenosylmethionine (SAM) to S-adenosylhomocysteine (SAH), an indicator of methylation capacity, were significantly decreased in the autistic children relative to age-matched controls. In addition, plasma levels of cysteine, glutathione, and the ratio of reduced to oxidized glutathione, an indication of antioxidant capacity and redox homeostasis, were significantly decreased. Differences in allele frequency and/or significant gene-gene interactions were found for relevant genes encoding the reduced folate carrier (RFC 80G > A), transcobalamin II (TCN2 776G > C), catechol-O-methyltransferase (COMT 472G > A), methylenetetrahydrofolate reductase (MTHFR 677C > T and 1298A > C), and glutathione-S-transferase (GST M1). We propose that an increased vulnerability to oxidative stress (endogenous or environmental) may contribute to the development and clinical manifestations of autism. (c) 2006 Wiley-Liss, Inc.

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Harrington JW, Rosen L, Garnecho A, Patrick PA. **Parental perceptions and**

**use of complementary and alternative medicine practices for children with autistic spectrum disorders in private practice.** J Dev Behav Pediatr. 2006 Apr;27(2 Suppl):S156-61.

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#### Abstract

The prevalence of autistic spectrum disorder (ASD) in the United States is approximately 1 in 150 children. Many health care providers are unaware of parental beliefs and treatments, both medical and complementary, that parents use for their child with ASD. Understanding these beliefs and practices concerning diagnosis, cause, and utilization of medical and complementary care may help physicians provide better comprehensive care. Parents of children with ASD from 2 private practices—one in New York and one in New Jersey—were mailed a 6-page, self-administered survey. In addition to demographics and ASD type, the survey asked parents who diagnosed their child and if there was a perceived delay in that diagnosis; whether they believed there was any causal reason for their child's autism; what chronic symptoms, if any, their child experiences; and, if they had used any complementary and/or alternative therapies and at whose recommendation. Respondents included 77 of the 150 parents (51%) contacted. Most children were diagnosed by a neurologist and/or developmental pediatrician (54% and 47%, respectively). Average perceived delay in diagnosis was 18 months. Parents most frequently cited immunizations (54%), genetic predisposition (53%), and environmental exposure (38%) as a cause of their child's autism. Approximately half of children were reported as having at least one gastrointestinal, neurological, and/or allergic symptom; more than a third had immunological symptoms. Almost all parents (95%) indicated some use of complementary and alternative medicine (CAM) therapies, with most of the self-reported referrals generated from a physician or nurse (44%). Systemic complaints, parental beliefs, and use of CAM practices warrant open discussion by all health care professionals who provide care to this population.

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James SJ, Cutler P, Melnyk S, Jernigan S, Janak L, Gaylor DW, Neubrandner JA. **Metabolic biomarkers of increased oxidative stress and impaired methylation capacity in children with autism.** Am J Clin Nutr. 2004 Dec;80(6):1611-7.

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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.

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### **FATTY ACIDS:**

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Ming X, Stein TP, Brimacombe M, Johnson WG, Lambert GH, Wagner GC. **Increased excretion of a lipid peroxidation biomarker in autism.** *Prostaglandins Leukot Essent Fatty Acids*. 2005 Nov;73(5):379-84.

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Abstract

It is thought that autism could result from an interaction between genetic and environmental factors with oxidative stress as a potential mechanism linking the two. One genetic factor may be altered oxidative-reductive capacity. This study tested the hypothesis that children with autism have increased oxidative stress. We evaluated children with autism for the presence of two oxidative stress biomarkers. Urinary excretion of 8-hydroxy-2-deoxyguanosine (8-OHdG) and 8-isoprostane-F2alpha (8-iso-PGF2alpha) were determined in 33 children with autism and 29 healthy controls. 8-iso-PGF2alpha levels were significantly higher in children with autism. The isoprostane levels in autistic subjects were variable with a bimodal distribution. The majority of autistic subjects showed a moderate increase in isoprostane levels while a smaller group of autistic children showed dramatic increases in their isoprostane levels. There was a trend of an increase in 8-OHdG levels in children with autism but it did not reach statistical significance. There was no significant correlation between the levels of the biomarkers and vitamin intake, dietary supplements, medicine, medical disorders, or history of regression. These results suggest that the lipid peroxidation biomarker is increased in this cohort of autistic children, especially in the subgroup of autistic children.

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Shaw W, Kassen E, Chaves E. **Increased urinary excretion of analogs of Krebs cycle metabolites and arabinose in two brothers with autistic features.** Clin Chem. 1995 Aug;41(8 Pt 1):1094-104.

Department of Pathology, Children's Mercy Hospital, University of Missouri-Kansas City 64108, USA.

#### Abstract

A marked increase in analogs of Krebs cycle metabolites was found in the urine of two brothers with autistic features. These metabolites included citramalic, tartaric (3-OH-malic), and 3-oxoglutaric acids and compounds tentatively identified as a citric acid analog and partially identified as a phenylcarboxylic acid by the fragmentation pattern of the trimethylsilyl (TMS) derivatives of the compounds and mass shifts of the same compounds derivatized with perdeuterated N,O-bis(trimethylsilyl)trifluoroacetamide. The molecular mass of the TMS derivative of the tentatively identified citric acid analog was 596 Da, based on a finding of a significant M - 15 ion at m/z 581. The citric acid analog was excreted in quantities as high as 137 mmol/mol creatinine, based on the response factor of citric acid as a surrogate calibrator. A carbohydrate with a retention time and mass spectrum identical to arabinose was also found in high concentrations in the urine of these brothers.

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Kolmen BK, Feldman HM, Handen BL, Janosky JE. **Naltrexone in young**

**autistic children: a double-blind, placebo-controlled crossover study.** J Am Acad Child Adolesc Psychiatry 1995 Feb;34(2):223-31

Child Development Unit, Children's Hospital of Pittsburgh.

**OBJECTIVE:** This study evaluated the efficacy and safety of naltrexone, an opiate blocker, in the treatment of autism. **METHOD:** Thirteen children with autistic disorder, aged 3.4 to 8.3 years (mean 5.4), were studied in home, school, and outpatient laboratory. Naltrexone, 1.0 mg/kg, was given daily in a randomized, double-blind, placebo-controlled crossover design. Dependent measures included parent and teacher Clinical Global Impressions (CGI), Conners Rating Scales, and Naltrexone Side-Effects (SE) Rating Scale; laboratory CGI, movement actometer readings, and a 10-second interval recording system analysis of on-task, communication initiations, disruptive behavior, and self-stimulation. **RESULTS:** Eight of 13 subjects improved in two or more settings. Changes in parent measures (CGI, Conners Impulsivity-Hyperactivity Factor, and SE-Restlessness) and Teacher CGI achieved statistical significance. Teacher SE-Restlessness and initiation of communication in the clinic showed a trend toward improvement. Actometer readings improved in two children who were very active at baseline. Adverse side effects were behavioral, mild, and transient. Administering the bitter tablet was a challenge. **CONCLUSIONS: Naltrexone offers promise as an agent for modest improvement of behavior and social communication in young children with autism.** Parent and teacher measures can be useful in outpatient trials to evaluate change.

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Leboyer M, Bouvard MP, Launay JM, Recasens C, Plumet MH, Waller-Perotte D, Tabuteau F, Bondoux D, Dugas M. [**Opiate hypothesis in infantile autism? Therapeutic trials with naltrexone**] [Article in French]. Encephale. 1993 Mar-Apr;19(2):95-102.

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Abstract

The opioid hypothesis suggests that childhood autism may result from excessive brain opioid activity during neonatal period which may constitutionally inhibit social motivation, yielding autistic isolation and aloofness (Panksepp, 1979). This hypothesis has now received strong support and is currently based on three types of arguments: (1) similarity between autistic symptomatology and abnormal behaviors induced in young animals by injections of exogenous opioids, such as increasing social aloofness and decreasing social vocalization; (2) direct biochemical evidence of abnormalities of peripheral endogenous opioids being reported in autism and (3) therapeutic effects of the

long lasting opioid receptor blocking agent naltrexone in autism. In this article, we give description of open and double-blind studies of naltrexone in autism. Naltrexone has been tested in several open studies. We performed an open trial with naltrexone in 2 autistic girls, displaying serious self-injurious behavior, reduced crying and a marked preference for salty and spicy foods, symptoms that could be related to a dysfunction of the opioid system. **With dosages of 1 mg/kg/day, we observed an immediate reduction of hyperactivity, self-injurious behavior and aggressiveness, while attention improved. In addition, social behaviors, smiling, social seeking behaviors and play interactions increased** (Leboyer, Bouvard et Dugas, 1988). Campbell et al. (1988) has also reported a tranquilizing and a stimulating effect in 6 out of 8 children with autism. We did confirm these preliminary results in a double-blind study performed on 4 children with autism. In a cross-over double-blind study, three dosages of naltrexone (0.5, 1 and 2 mg/kg/day) and placebo were compared.

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