# ASA's 36th National Conference on Autism Spectrum Disorders (July 13-16, 2005)

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## #1181- Oxidative Stress in Autism: What Parents Should Know

Recent studies show greater oxidative stress in children with autism. Other studies show that anti-oxidant nutrients can impro symptoms. Parents need to be familiar with the concept of “oxidative stress”, evidence of greater oxidative stress in autism, a nutritional steps which may reduce oxidative stress in their children.

**Presenter:** ***Woody R. McGinnis, MD*** - Dr. McGinnis began learning about nutrition and behavior through his son. He coc Oxidative Stress in Autism Study, which measures oxidative markers in the urine, blood and brain of children organized the 2005 Oxidative Stress in Autism Symposium at the Institute for Basic Research in New York.

- Explain “oxidative stress” and oxidative tissue damage.
- Evidence of greater oxidative stress in children with autism.
- How other abnormalities are consistent with oxidative stress.
- Evidence of benefit from anti-oxidant nutrients.
- Nuts-and-bolts primer on anti-oxidant nutrition.

Chemically, oxidation is loss of electrons. When oxidation is rapid, it may result in actual flames, as when wood burns. M oxidation may result in the browned surface of an apple, or the rancidity of oils. The building blocks of cells—fats, proteins, a acids—are prone to oxidation, which alters structure and function and results in tissue injury.

Compounds which cause oxidation are called oxidants. Some oxidants leak into the cells as natural by-products of cellula In addition, toxins entering the body—pollution, chemicals, heavy metals, insecticides, flavor-enhancers in foods—act as oxid excess, nutrients such as copper and iron can act as oxidants. Some of the oxidants which injure cells are called free-radical oxidants are free-radicals.

Fortunately, the body has a defense system to neutralize oxidants. The components of this system are anti-oxidant. Thes important dietary antioxidants such as vitamins C, E and A. Other nutrients serving important anti-oxidant roles include B vita selenium, magnesium, carnosine and carnitine. The body also manufactures special molecules to quench oxidants. These i glutathione (GSH), metallothionein (MT), melatonin, estrogen, ceruloplasmin, transferrin, and important anti-oxidant enzymes peroxidase (GSHPx), superoxide dismutase (SOD), and catalase.

Oxidative stress occurs when oxidants exceed the anti-oxidant defense. Oxidized cell parts in urine, blood and tissue suc direct measurements of oxidative stress. For example, the level of oxidized lipids (“lipid peroxides”) in blood is used as a bior oxidative stress.

Indirectly, we also can get an idea about oxidative stress by measuring levels of anti-oxidant nutrients, anti-oxidant molecu GSH, or anti-oxidant enzymes. Lower levels of one or more of these anti-oxidant defenses tends to suggest greater oxidative Higher levels of oxidants, such as free-radicals and toxins, suggest higher levels of oxidative stress.

Convincing data demonstrate greater oxidative stress in groups of children with autism, as compared to controls. Oxidized in blood (lipid peroxides in both red-cells[1] and serum[2]) and urine (isoprostanes[3]) are significantly elevated in autism. Autistic significantly increased lipofuscin[4] after age seven, and a more specific oxidative marker is found in cortical dendrites in even

subjects.[5]

Indirect markers are highly consistent with increased oxidative stress. Plasma levels of vitamins C, E, A and red-cell zinc, and selenium are lower.[6] Vitamin B6 activity by EGOT[6] and P5P[7] determination are lower. Protective anti-oxidant molecules plasma glutathione and GSH/GSSG,[8] red-cell GSHPx,[9,10] plasma GSHPx,[10] red-cell SOD,[10] platelet SOD,[9] red-cell catalase ceruloplasmin and serum transferrin.[2]

Oxidant levels are higher in groups of autistic children. Multiple studies demonstrate much higher production of the nitric o free-radical ($NO^{\cdot}$) in autism.[11,12,13] Another finds higher xanthine oxidase,[1] which predicts greater generation of other free-ra Environmental toxins are higher: perchlorethylene, hexane and pentane in plasma; mercury, lead and arsenic in red cells.[6] copper[14] and provoked urinary mercury[15] are higher.

Laboratory and clinical findings are consistent with greater oxidative stress. For one, brain and gut pathology are well-desc autism, and these tissues are highly sensitive to oxidative injury. In addition, specific data suggest lesser energy production a excitoxicity in autism, and these predict greater oxidative stress. Finally, anti-oxidant nutrients have been shown to improve a behavior.

A fundamental, reciprocating relationship exists among oxidative stress, low energy production, and excitotoxicity. Deficits production on brain scans[16] and altered lactate,[17,18] pyruvate,[19] ammonia and carnitine[20] levels suggest decreased energy children with autism. Alterations in glutamate metabolism [6,17,21,22] are consistent with greater excitotoxicity.

Reduction of autistic behaviors after treatment with high-dose vitamin C (8 grams/70kg/d)[23] or carnosine (400mg twice dai reported in double-blind, placebo-controlled trials. Other studies demonstrated improvement in autistic behaviors with high-d in combination with magnesium,[25,26] and these nutrients serve important anti-oxidant functions. There are increasing parent benefits from reduced glutathione, a classical antioxidant, as well as carnitine, a mitochondrial booster.

Oxidative stress is a plausible core mechanism in autism. Realistically, many years of research will be needed to prove th nutrients benefit autistic behavior by reducing oxidative stress—and in which children. Given the promising early results with a and the benign nature of nutritional intervention, more parents are electing to try the nutritional approach now, before their chi much older. There is a safe and systematic way to try nutrients, and if nothing else, addressing lower nutrient levels may impr general health. After all, excess oxidative stress is a general health risk.

Laboratory testing can be useful in the nutritional approach to autism. Stool studies help identify microbial overgrowths, wh nutrient absorption and increase systemic toxins. Red-cell mineral measurement identifies low or lowish levels of zinc, seleni magnesium, correction of which should be confirmed by re-testing after supplementation. Similarly, low or lowish plasma vita are of major clinical concern. Urinary organic acids provide useful information, help identify elusive fungal and anaerobic ove gut. IgG blood testing for food allergy is often useful.

A multi-vitamin/mineral combination (without iron or copper, rarely necessary) provides broad-based nutritional support, ar well-tolerated, is a good way to start supplementation. Additional nutrients can be added to achieve optimal total doses on ar basis. It is important to remember that nutrients work gradually, and combinations are important.

If a rationale exists for giving a particular nutrient, it is advisable to continue giving it as long as it is well-tolerated, adding Jumping from one nutrient to another is much less advisable. If a nutrient is not well-tolerated, a lower dose may be necessa the nutrient can be tried again later. Careful records should be kept, and the child should be observed for a day or two for adv before adding the next nutrient.

Vitamin E, preferably as natural mixed tocopherols, is safe and well-tolerated in doses between 200-1200 IU daily. It takes we build-up vitamin E levels, and asborption is not always good. Generous dosing is warranted in children with autism.

Vitamin C 500-5000 mg daily, is probably best divided into morning and evening doses, which may be limited by the stool-sof tendency of vitamin C (which may be a desirable side-effect in constipated children).

Calcium 1000 mg daily as citrate, but NOT from bone-meal or oyster shell, is highly recommended. Calcium supplements in foods and drink are generally not highly absorbable, so children off dairy especially need extra calcium.

Magnesium 200-600 mg daily, is particularly important in children with low or borderline red-cell levels, seizures or hyperactiv children have real difficulty absorbing magnesium. Magnesium glycinate is highly-absorbable.

Selenium 100-400 mcg daily is very, very important—even borderline deficiency, as evident in red cells, can depress significa anti-oxidant enzyme GSHPx.

Zinc is a crucial nutrient in autism, and after careful observation of thousands of patients, clinicians are now comfortable with doses. For optimal absorption, zinc picolinate or citrate, 1-3mg/kg/day, is given away from other minerals and cereal grains ( bedtime vitamin C). Mean-or-above red-cell levels on follow-up testing are desirable.

Blood testing is used to assure that zinc dosing is not in excess. After a few months, plasma zinc should not exceed the upp normal, and serum copper should not fall below the lower limit of normal. To avoid artifact, zinc should not be given 24 hours testing. Higher zinc doses can suppress manganese, which can be given 5-20 mg/day.

Vitamin B6 (up to 1000 mg daily), or its activated form, pyridoxal-5-phosphate (P5P, up to 200 mg daily) in divided doses is s children with autism. A combination of P5P 50 mg + 100 mg of magnesium as glycinate, up to four times/day, is effective in n Zinc picolinate and P5P should be given at different times, to avoid binding.

Fatty acids are commonly depleted in autism, and can be a powerful therapeutic tool. Red-cell membrane fatty acid analysis findings can help guide dosing of omega-3 (fish oil) and omega-6 (evening primrose oil, EPO). As a rule, it is desirable to tre anti-oxidant vitamins and minerals for 10-14 days prior to oils, since unchecked oxidative stress can increase oxidation of the generate toxic lipid peroxides. Many autistic children achieve optimal effects with a balance of both fish oil (to provide 200-80 and EPO (200-800 mg GLA). Fish oil should be used cautiously in children with underlying bleeding disorders.

Children with dry hair or skin, folliculitis, allergies or asthma may benefit from generous intial dosing with fish oil, part of wh given as cod liver oil, up to the vitamin A limit of 2500-5000 IU daily. Besides omega-3, cod liver oil contains natural vitamin A oil does not contain vitamin A. Smaller balancing doses of evening primrose oil may be useful.

If leaky gut, depressed mood, immune depression or poor growth predominate, EPO may be a first priority, with smaller do Balancing these oils is important— the published data demonstrate lower omega-3 in some children with autism, lower omeg and eventual depression of omega-6 DGLA [27] (which the body can make from the GLA in EPO) with only FO.

Reduced glutathione (GSH) by I.V. (or orally, up to 30 mg daily, in divided doses) is often helpful. Infrequent reversible advers oral GSH may be related to unchecked fungal overgrowths or inadequate zinc loading. N-acetyl cysteine (orally, or intravenc combination with vitamin C) may increase production of GSH.

Other B vitamins are being used successfully in autism. Vitamin B12 (1000-5000 mcg by mouth daily) and methyl cobalamin beneficial, possibly due to strong $NO^{\cdot}$-quenching effects of vitamin B12. Oral folinic acid may improve methylation and reduc stress. As with vitamin B6, both B12 and folate are susceptible to inactivation by oxidants. TTFD, a form of thiamine, may bo production and decrease oxidative stress. Niacinamide, the non-flushing form of vitamin B3, is a very potent oxidant-quenche physiologically relevant concentrations, and may prove useful in autism.

Mitochondrial boosters are potentially beneficial in children with autism. CoQ10 (10 mg/kg/d), carnitine (up to 50mg/kg/d), thi (15mg/kg/d), riboflavin (15 mg/kg/d) and pantothenate (15 mg/kg/d) can be given separately or in combination.

Nutritional needs and tolerances vary in children with autism, and may change. Important adjucts to supplementation inclu bowel overgrowths, addressing food intolerances (including a casein-gluten free trial, reasonable in all children with autism), of regular bowel movements, and avoidance of blood-sugar swings by minimizing sugar and other simple carbohydrates. A lo environment, with pure air, filtered water, and organic foods are highly desirable. Relaxing activities and environment are a hi children with autism—increasingly, science recognizes emotional stress as a direct cause of oxidative stress.

Lastly, some compounds found in foods just shouldn't be ingested by children with autism. Excitoxic flavor enhancers and (monosodium glutamate or MSG, hydrolyzed vegetable protein, “natural flavoring” in some prepared foods, and aspartame) s avoided absolutely in any population with increased oxidative stress. This precludes many fast-foods, prepared foods and se Foods containing nitrates or nitrites (as in preserved meats, bacon, ham, hot-dogs, pickles) are not advisable, since children known to have higher levels of these toxic derivatives of nitric oxide.

Besides paving the way for therapeutic applications, greater understanding of oxidative stress in autism may improve our on potential genetic and environmental causes of autism. For further information, refer to a peer-reviewed article on oxidative autism,[28] or the Proceedings of the 2005 Oxidative Stress in Autism Symposium. For numbered references mcginnis@mind.

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