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## **Digestive, Metabolic Problems Abound In Patients with ADHD, Autism**

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Editor in Chief

PORTLAND, OR- Attention Deficit Hyperactivity Disorder and autism are multifactorial biological disorders requiring a multimodal therapeutic approach that addresses the gastrointestinal, immunologic and metabolic problems usually associated with the behavioral abnormalities, said Jeff Bradstreet, MD, at the annual meeting of the American Holistic Medical Association.

"Conventional allopathic concepts define ADHD and autism as 'psychiatric' disorders. I think that's bunk. I look at ADHD and autism biologically," said Dr. Bradstreet, founder of the International Child Development Resource Center (ICDRC), a clinic and foundation that has treated over 2,000 children with ADHD or autism. "As an MD, I had to move toward naturopathic principles to learn how to treat these disorders."

Over the years, Dr. Bradstreet has developed sophisticated therapeutic protocols centered on correcting digestive problems, eliminating allergens and environmental toxins, and improving nutrition. Whenever possible, he prefers to treat these kids without pharmaceuticals. "I only use drugs as a rescue modality."

While ADHD and autism are related in many ways, and sometimes overlap, Dr. Bradstreet believes they are distinct conditions. He rejects the notion that autism is simply an extreme form of ADHD. However, he contends that both reflect altered brain and CNS function, which are the net result of environmental toxin overload, abnormal immunologic reactions, impaired hepatic detoxification, and GI dysfunction which can sometimes be extreme.

There is still plenty of debate over how to define these conditions and even more regarding their etiologies. But there is little argument regarding the sharply increasing incidence and prevalence. The most

recent estimate is that one in every five school aged boys in the US must take a stimulant to go to school. There are over 350 million doses of methylphenidate given to US schoolchildren every year.

Federal registries suggest there are between 9 and 12 million children with ADHD. Data from California indicate one in 160 school age children have some form of autism; the figures have doubled over the last four years. "Some of this may be overdiagnosis, but I think that most of it is not. It is very, very real."

Dr. Bradstreet and his colleagues believe ADHD arises from a combination of immunologic, allergic and digestive dysfunction that begins with damage to the child's immune system early in development. The injury may be due to environmental toxin exposure, but in the majority of cases, he believes mercury-containing vaccines do play a role. Thimerosal and aluminum in vaccines are intrinsically neurotoxic, and they can also modulate immune function.

Live viral vaccines contain as much as 25 mcg of mercury (as thimerosal) per dose. Young children receiving serial live viral vaccines get quantities of mercury that, on a body weight basis, exceed safe levels for US adult fish consumption.

Dr. Bradstreet and his colleagues recently completed a case control study showing a statistically significant correlation between mercury exposure at an early age and autism. Those who had the highest levels of mercury exposure had a 6.4-fold increased prevalence of autism than those at the lowest levels. There was no correlation between autism and lead or cadmium exposure. "It is not just vaccine mercury, but environmental mercury as well."

The vaccine etiology, though still highly controversial, has been gaining credence in recent years. A CDC-funded study recently showed a statistically significant difference in the prevalence of ADHD, autism, and tick disorders between individuals who received mercury-containing vaccines at 3 months, and those who did not. Analysis of data from the federal Vaccine Adverse Events Reporting System (VAERS) and the US Department of Education do show a linear correlation between the odds ratio for neurodevelopmental disorders and thimerosal exposure (Geier DA, Geier MR. *Pediatr Rehab.* 2003. 6 (2): 97-102).

However, two recent Danish population-based studies comparing rates of these disorders between hundreds of thousands of individuals

vaccinated with thimerosal-containing versus thimerosal-free vaccines, failed to show any correlation (Hviid A, et al. JAMA. 2003; 290 (13): 1763-6, Madsen KM, et al. Pediatrics. 2003; 112 (3 pt. 1): 604-6). Most conventionally-trained pediatricians hold that there is little risk of autism from vaccines, especially thimerosal-free vaccines. They argue that if there is any risk, it is probably very small, and that the benefits of vaccination far outweigh any potential risks.

Dr. Bradstreet, the father of an autistic child, strongly disagrees. "There are still no truly mercury-free vaccines," he said, suggesting that this may explain the absence of a correlation in the Danish studies. "We are making progress and they are getting better. But there's still a lot of mercury out there."

Live virus vaccines, such as the one for measles are particularly problematic, said Dr. Bradstreet. "The way it is injected, the virus gets immediate access to the tissues in which it prefers to proliferate the lymph nodes and CNS-and escapes immune system clearance. As a result, residual virus can become a problem. In one recent study, 50% of a cohort of children with autism had cerebrospinal fluid antibodies to measles virus proteins found in the MMR vaccine. Many ADHD/autism children also have a unique form of irritable bowel disease in which proteins traceable to vaccine strains of measles are found.

While there is still much room for debate about the connection between vaccines and neurodevelopmental disorders, there is a growing consensus that children with ADHD and autism typically have gastrointestinal problems, and that the two are related.

The GI tract in most of these patients is, to put it bluntly, a total mess,said Dr. Bradstreet. He insisted that without cleaning up the gut problems, it is impossible to make headway in resolving ADHD and autism. Lower GI dysfunction, enzyme deficiencies and impairments of hepatic detoxification pathways are very common.

Patients typically excrete large amounts of sulfate in their urine, sometimes as much as 10 times more than normal children. The cause is yet not known, but it results in impairment of sulfate-dependent hepatic detoxification pathways. These patients also excrete cysteine, a key amino acid for glutathione production. Cysteine wasting is a characteristic of residual viral infection, and it results in compromise of glutathione-dependent detoxification pathways. The net result is that these individuals can't break down and excrete toxins.

Pancreatic enzyme deficiency is very common; Dr. Bradstreet noted that approximately 75% of the children he treats have significant deficiencies of key pancreatic enzymes. As a result, they do not digest proteins properly, setting the stage for both upper and lower GI problems.

Researchers at the department of pediatric gastroenterology, University of Maryland studied 36 autistic children via endoscopy, biopsy, and intestinal and pancreatic enzyme analysis. They found that 69% had grade I or II esophageal reflux and inflammation, 42% had chronic gastritis, 67% had duodenitis, and 58% had low carbohydrate digestive enzyme levels (Horvath K, et al. *J Pediatr.* 1999; 135 (5): 559-63).

Diarrhea and constipation are common in these patients. Some kids tend to have more diarrhea, while others have constipation so extreme they develop impactions. "You can sometimes feel these huge fecal masses if you palpate their abdomens," said Dr. Bradstreet. This can be particularly problematic because in essence, they are storing large loads of toxins, further burdening their already compromised hepatic detoxification pathways.

Many ADHD/autism patients have "leaky gut" syndrome, characterized by a breakdown of the tight junctions between endothelial cells in the gut lumen. This is evidenced by the presence of lactulose in their fecal material (D'Eufemia P, et al. *Acta Pediatr.* 1996; 85 (9): 1076-9). A highly permeable gut wall allows passage of all sorts of antigenic proteins, toxins, and pathogens into the circulation.

Dr. Bradstreet is particularly concerned about "exorphins," protein fragments from the incomplete digestion of grain gluten and casein. Some of these protein fragments, like beta-casomorphins and gluteomorphins, are neuroactive and able to bind to opioid receptors in the brain. In a child with a leaky gut, these exorphins easily pass into circulation, and since hepatic clearance of opioid neurotransmitters is already compromised, the exorphins hang around for a long time. He believes they are driving factors in the cognitive symptoms and abnormal behaviors of ADHD and autism (Wakefield AJ, et al. *Aliment Pharmacol Ther.* 2002; 16 (4): 663-74).

Some of the most compelling work linking digestive system problems with neurobehavioral disorders like ADHD and autism comes from the work of Andrew J. Wakefield and his Inflammatory Bowel Disease

Study Group at the Royal Free and University College Medical School, London. His team performed ileocolonoscopy with biopsies on 60 children with developmental disorders including autism, ADHD and Asperger's syndrome, as well as 50 unaffected control subjects.

They found ileal lymph node hyperplasia in 93% of the affected children, but in only 14% of the controls, and colonic node hyperplasia in 30% of the affected kids, but 5% of the controls. Close to 90% of the kids with developmental disorders had chronic colitis, versus only 4% of the controls (Wakefield AJ, et al. Am J Gastroenterol. 2000; 95 (9): 2285-95). This builds on an earlier study of 12 children, all of whom showed nodular hyperplasia and colitis (Wakefield AJ, et al. Lancet. 1998; 351 (9103): 637-41).

Clostridium, which can secrete a number of neuroactive toxins, also plays a role in some patients. Patients with late onset autism sometimes have increased numbers of clostridial species in the gut. Dr. Bradstreet described the bizarre case of a dog that inadvertently ate feces from an autistic child: the dog went into a coma for 7 days. "Researchers at the University of Michigan are studying feces from this child to see what might have caused this extreme reaction. We think it might be clostridial toxins."

Management of the complex multi-system problems characteristic of ADHD, autism and other developmental problems is a major challenge for physicians and families of these children. Dr. Bradstreet centers his approach on the following goals: improvement of GI function, restoration of normal immune function, elimination of heavy metals and other toxins, and supplementation to optimize hepatic, immunologic, neurologic, and cognitive function.

He does use DMSA chelation to eliminate mercury and other heavy metals, and said that over 70% of these children will show major improvements in behavioral symptoms just from this alone. "It is the number one treatment as rated by the parents; no drug even comes close."

Other treatments that help with detoxification include:

Selenium: At a dose of 25 mcg/day, this mineral facilitates detoxification by binding to mercury by forming selenium-mercury complexes that can be safely excreted in the urine. It is also an essential cofactor for synthesis of glutathione peroxidase, a key antioxidant enzyme.

Milk Thistle (*Silybum marianum*): Standardized preparations of 70-80% silymarin, an important bioactive component of this plant, were shown to improve liver function in patients with solvent-induced liver damage. There is also a study of 166 children with chronic liver disorders, 70% of whom showed liver function improvements while taking silymarin.

N-Acetyl Cysteine (NAC): Since most patients with ADHD or autism are cysteine deficient, this is a cornerstone of treatment. NAC is a precursor of glutathione, an essential player in hepatic detox pathways. Dr. Bradstreet recommends starting with a low dose of 25 mg/day and gradually increasing up to 200 mg daily.

Calcium-D-glucarate (as Betaine): This salt of D-glucaric acid inhibits beta-glucuronidase, and increases net elimination of toxins and steroid hormones via glucuronidation, a critical step in Phase II hepatic detoxification. Begin with 150 mg, and increase to 1,000 mg per day.

Alpha Ketoglutarate (AKA): These patients often show elevated ammonia levels, derived from abnormal GI flora. AKA helps detoxify ammonia. It is also a precursor of glutamine which helps heal the gut mucosa. The dose range is 250-750 mg/day.

Taurine: This sulfonic amino acid is involved in formation of bile salts, which are essential for toxin elimination. Taurine also plays a role in neuromodulation, and tends to have a calming effect on ADHD patients. Begin with 100 mg and build up to 1,000 mg/day.

Methionine: This amino acid binds heavy metals, and adds methyl groups to xenobiotics, aiding in their excretion. Supplemental methionine increases production of several cytochrome P450 enzymes. The dose range is 100-400 mg.

Given that many of these patients have enzyme deficiencies, enzyme replacement using fixed combinations of plant-based enzymes is a cornerstone of therapy. A recent clinical trial in which 29 children with autism spectrum disorders were given an enzyme formula containing exo- and endo-peptidases, showed measurable improvements on 13 cognitive and behavioral parameters.

Dr. Bradstreet strongly recommends a gluten and casein-free diet. While not a "cure," this can certainly have a big impact (Knivsberg AM, et al. *Nutrit Neurosci.* 2002; 5 (4): 251-261). He also advised

eliminating as many common allergenic foods as possible. This includes corn, wheat, soy and nuts.

Other important nutrients and supplements that can improve digestive, immunologic and neurologic function in these patients include:

**Omega-3 Fatty Acids:** "This is a must. These patients are almost always deficient." Omega-3s are critical components of neuronal membranes and they are essential for normal neurologic development. 1,000 mg per day is a reasonable starting dose, but don't hesitate to go as high as 3,000 mg.

**Probiotics:** Once the severe GI abnormalities are cleared, it is important to re-seed the gut with healthy flora. Probiotic supplements are the easiest way to accomplish this.

**Vitamins A, C, and E:** These "letter" vitamins, as well as beta-carotene are all important antioxidants, and patients with ADHD/autism are usually deficient. While a good multivitamin will probably provide most of what these patients need, it doesn't hurt to add additional vitamin C, which supports glutathione-mediated detoxification pathways.

**B Vitamins:** B6 is probably the most well-studied vitamin in management of ADHD/autism. It is essential for healthy brain function, and patients are typically deficient. Since 1965, there have been 18 trials of high-dose B6. Overall, the data suggest that this will help 50%, while the other 50% show no benefit. Some studies suggest that B6 should be taken with magnesium.

**Zinc and other minerals:** Both serotonin and melatonin are synthesized via zinc-dependent enzymes. Zinc-deficient children are often irritable, sullen and difficult to soothe. ADHD/autistic patients are usually deficient in zinc, as well as magnesium, iron and calcium.

Dr. Bradstreet has also found pycnogenol, a derivative of French maritime pine trees, and L-theanine, derived from green tea, to be effective in improving cognitive function and helping to produce a calm but focused attention in these patients. Co-enzyme Q10, L-carnitine, L-carnosine and dimethyl aminoethanol (DMAE) are also helpful in improving cognitive function.