**Review**

# A Call for Action: Recognizing and Treating Medical Problems of Children with Autism

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**The care of children with autism requires attention to medical problems which they may develop. Significant subsets of children with autism have intestinal inflammation, digestive enzyme abnormalities, metabolic impairments, oxidative stress, mitochondrial dysfunction, and immune problems which range from immune deficiency to hypersensitivity to autoimmunity. The author works within a paradigm that views autism as a body wide, multi-system disorder. Behavioral symptoms may be signs of underlying pain in children with communication problems and require attention to underlying pathology rather than relying on behavioral measures to extinguish the behaviors. Opportunities for improving quality of life and autistic symptoms are found by using a combination of detailed histories, physical exams and laboratory evaluations to uncover clues about underlying medical issues that need to be treated. The current prevalence of autism and the suffering of the children and families involved call for action by primary care physicians working in collaboration with researchers, specialists and parents if these children are to receive appropriate medical care.**

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## INTRODUCTION: A MORAL IMPERATIVE TO ACT

Autism currently affects 1 in 88 children in the United States. When just males are considered, the diagnosis is made in 1 in 54 boys.[1] Families are overwhelmed by this pandemic, as evidenced by high divorce rates among parents of children with autism.[2] Despite the prevalence of autism, most primary care physicians feel unprepared to treat it.[3] Our perspective is that, as adults and as medical professionals, we have a moral imperative to address the suffering of these children and their families.

## THE ORIGINAL DESCRIPTIONS OF AUTISM

Autism was originally described as a new entity in 1943 by Leo Kanner, a prominent child psychiatrist from Johns Hopkins.[4] Autism has been classified as a psychiatric illness and characterized by behavioral symptoms for diagnosis by DSMIV criteria: impairments in communication; problems with social interactions; and repetitive, restricted or stereotyped behaviors.[5] However, nothing in the criteria precludes medical problems or speaks to causation. All of the children in Kanner's original cohort of 11 had medical problems.[6] For years, physicians have largely ignored these medical problems, instead choosing to focus on behavioral problems of these children and even perceived inadequacies of their "refrigerator mothers," a term Bettleheim famously coined.[7]

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## A NEW PARADIGM

At the Rimland Center for Integrative Medicine, we have evaluated children with autism from 20 states and 5 countries. We operate under a different paradigm that views autism as a constellation of behaviors that might result from a number of different pathways or etiologies, and be associated with underlying medical problems that are ripe for intervention. We recognize the importance and context of genetic predispositions and environmental components within the framework of child development.[8] In many cases, improvement of autistic symptoms is achieved by a combination of nutritional recommendations, prescription medications and addressing the underlying medical conditions seen in these children.

Medical problems that have been identified in children with autism and are amenable to intervention include: intestinal pathology,[9-11] metabolic problems,[12,14] immune dysregulation,[15-20] oxidative stress,[21-23] and mitochondrial dysfunction.[24]

## GASTROINTESTINAL PATHOLOGY AND CRIES FOR HELP

Children with autism often have gastrointestinal symptoms. Many adopt a characteristic posture designed to put pressure on the lower abdomen, which is an adaptive behavior designed to reduce pain.[25] Some are unable to generate enough pressure to defecate while sitting on a toilet and adopt a squatting posture as an adaptive strategy to produce a Valsalva maneuver.

A sub-set of children with autism have a dramatic increase in tumor necrosis factor alpha and interferon gamma cytokines in the duodenal lamina propria layer. In addition to this increase in pro-inflammatory cytokine messages, these children demonstrated a depletion of the counter regulatory cytokine interleukin 10, which is designed to reduce chronic inflammation.[26] From a clinical perspective, it is valuable to consider intestinal inflammation in the differential diagnosis of children with autism who present with diarrhea, constipation, alternating diarrhea and constipation, sleep disturbances, behavioral outbursts, or unusual posturing.

Some of the intestinal pathology that might exist in children with autism includes: histologic evidence of eosinophilic esophagitis,[27] small bowel inflammation,[28,29] blunting of intestinal brush borders[30] and abnormal intestinal permeability.[31,32] Intestinal pathology may present with extraintestinal manifestations. The classic example is celiac disease. A sub-set of patients presents with gluten ataxia[33] or neuromuscular weakness.[16] Extraintestinal features of celiac disease include alopecia, arthropathy, depression, dental enamel hypoplasia, folate deficiency anemia, follicular keratosis, and vitamin K deficiency.[35]

Clinicians treating autism must be ever-vigilant for the presence of organic pain in children who have limited ability to communicate their agony. Gastrointestinal status has been positively correlated with severity of autism in children.[36] Clinicians who evaluate children with autism should consider self-abusive behavior as a possible indicator of pain, difficulty toilet training as potential gut pathology and trouble sleeping as a sign of gastrointestinal reflux or abdominal pain until proven otherwise.[37,38] A consensus report describing the evaluation of GI disease in children with autism provides guidance for practicing pediatricians and family physicians.[39] Clinical tools such as the Bristol Stool Form Scale[37] help families communicate more specifically with clinicians to devise effective treatment strategies for constipation and diarrhea.

Constipation, which may be associated with megacolon,[41] can be a cause of discomfort and behavioral outbursts. In the author's experience, non-pharmacologic treatments such as magnesium citrate, Vitamin C. and aloe vera juice can help achieve the goal of daily, soft, easy-to-pass bowel movements.

Diarrhea may be associated with malabsorption related to digestive enzyme deficiencies[39] or inflammation. Evaluation may include testing stool lactoferrin or white blood cells as a marker of inflammation or performing a comprehensive digestive stool analysis to assess digestive status and composition of gut flora. Digestive enzymes can be measured directly during endoscopy, which can also assess inflammation and specific pathology.

The microflora of children with autism differs from the gut flora of neurotypical children.[43-45] Children with autism have different ratios of bifidobacter and firmicutes than neurotypical controls.[44] Firmicutes phyla includes clostridia, lactobacillus and streptococci.[46] Probiotics may be used to produce antimicrobial substances, enhance phagocytic and natural killer cell activity, stimulate secretory IgA, and block adhesion of pathogens and toxins.[47] Saccharomyces boulardii, a beneficial yeast which compete with Candida spp., also releases a protease that cleaves clostridia difficile toxin A, suppresses bacterial overgrowth and host cell adherence, and secretes proteins that inhibit production of KappaB.[48] Probiotics are recommended for all children with autism in the author's practice.

## METABOLIC ABNORMALITIES AND TARGETED INTERVENTIONS

Metabolic problems have been well-described in children with autism.[12,49] Methylation and transulfuration play a crucial role in the synthesis of neurotransmitters, the generation of creatine, cell differentiation, embryonic development and the genesis of cell membranes. Moreover, disruption of methylation biochemistry can have a profound effect on epigenetics. One way in which gene expression is controlled is through the attachment of a methyl group, which silences the gene. DNA methylation occurs at the cytosine bases of eukaryotic DNA via DNA methyltransferase enzymes. Methylation abnormalities can be associated with diseases such as cancer, lupus and certain birth defects.[11]

Compared to neurotypical children, children with autism have lower methionine, S adenosyl methionine and homocysteine.[12] Children with autism have a 72% reduction in glutathione.[14] Glutathione plays a crucial role in detoxification biochemistry, repair of gut epithelium, support of mitochondria and T cell function, as well as being the primary intracellular anti-oxidant in humans. Microglia and astrocytes need glutathione to protect neurons.[50,52] Both methionine cycle and transulfuration metabolites improve after supplementation with folinic acid, betaine and methylcobalamin.[14]

Due to single nucleotide polymorphisms that impair transport into the cell of methylcobalamin (transcobalamin 2) or folinic acid (reduced folate carrier)[46] children with autism may have high levels of B12 or folate in the blood. Supplemental folinic acid and methylcobalamin may appear paradoxical to a primary care clinician, but the extracellular B12 and/or folate cannot enter the cell, therefore this treatment is appropriate and effective in the author's experience. Children with autism have increased oxidative stress.[49] Strategies to treat oxidative stress include: 5-methyltetrahydrofolate to overcome an inability to convert the inactive form of folic acid to the active form, methylcobalamin injections to help the remethylation of homocysteine to methionine, and pyridoxil-5-phosphate with magnesium to facilitate the synthesis of cysteine and ultimately, glutathione.

A sub-set of children with autism have mitochondrial dysfunction, which can be inherited or acquired. Some causes of mitochondrial impairment include: oxidative stress,[12] poor nutrition,[53] propionic acid from clostridia,[51] as well as pesticides, diesel exhaust and PCBs.[55] Heavy metals such as

lead, arsenic, cadmium, aluminum and mercury have also been implicated in mitochondrial damage.[56] Twelve studies have reported developmental regression in children with autism who have abnormalities in mitochondrial function.[57] One case series of children with autism and mitochondrial disorders reported regression with catabolic stress in 7 of 25 of the cases.[58] Fever in children with mitochondrial disease has been suggested as a risk factor for autistic regression.[59,60] The evaluation of mitochondrial dysfunction includes: serum lactate and pyruvate, ammonia, creatinine kinase, and free and total carnitine. Analysis of amino acids shows an elevated alanine to lysine ratio while analysis of organic acids shows elevated fatty acid metabolites.[61]

Clinicians who care for children with autism should consider mitochondrial dysfunction when the following clinical signs are present: low muscle tone, constipation, fatigue, evidence of oxidative stress, or regression with vaccines[62] illness, fever, anesthesia, or sources of catabolic stress.

## IMMUNE DYSREGULATION AND OPPORTUNITIES FOR TREATMENT

Children with autism have a wide variety of immune problems.[63] Immune deficiency,[13] hypersensitivity[64] and autoimmunity[65,66] have all been described. Immune dysregulation may reflect phenotypic differences in children with autism who may have either enhanced autoimmunity or reduced immune function. One common pattern is increased activation of the TH1 and TH2 arms of the adaptive immune response without a compensatory increase in regulatory interleukin-10.[12] Autistic children with poor natural killer cell function are at risk for bacterial, viral and fungal infections.[13] Some children with autism who have chronic gastrointestinal symptoms also have distinct innate immune abnormalities.[67]

Clinicians caring for children with autism should be alert for clues such as allergic shiners, atopic dermatitis, fungal skin infections, oral thrush and warts. Evidence of immune dysregulation includes: increased IgE, IgA deficiency, lymphopenia, evidence of autoimmunity and abnormal natural killer cell function.

One rewarding aspect of identifying and addressing immune dysregulation, in addition to relieving pain and suffering, is that improvements in behavior may be seen. Patients with autism may have decreased serum levels of transforming growth factor-beta1.[68] Lower levels of TGF-beta correlated with increased severity of behavioral changes.[69] Behavioral symptoms of autism and impairments in focus and concentration in children with ADHD may correlate with pollen counts[70] and therefore be amenable to classic interventions with allergy medications and environmental controls.

## CONCLUSIONS: REWARDS OF MEETING THIS GREAT CHALLENGE

What a privilege to change the trajectory of a child's life! Medical problems clearly cause pain and suffering in children with autism. These children may react with aberrant or self-abusive behaviors which disrupt entire families. By learning how to evaluate and treat their medical problems, we can potentially improve quality of life for both the patients and their families. By addressing underlying pathology, we can intervene in abnormal vicious cycles of chronic inflammation, metabolic dysfunction, and immune dysregulation. By applying what we learn from ongoing research, we have a golden opportunity to improve the child's physiology to perform such vital functions as digestion and absorption of nutrients, to restore complicated cycles of methylation and transulfuration and to help restore balance to the innate and adaptive immune system.

What a reward to see a child in chronic pain happy and smiling after gluten is removed from his diet! What an honor to be thanked by a parent for "giving me my child back." What a thrill to see a four year old who presented to our center with a vocabulary of five words say the pledge of allegiance less than a year later!

Caring for the chronic and complex problems of children with autism does not fit well into our current medical system, which rewards high volume productivity characterized by short patient visits which culminate in a prescription for an acute problem. Caring for the devastating problems of children who mean the world to their families fits very well into the model of physician as healer and teacher, which many physicians thought they were adopting when they went to medical school. Physicians and parents can act under this paradigm to address each individual child's medical needs in a holistic fashion, thereby treating the human body as the interconnected, synchronous entity it is and helping to restore health.

**COFLICT OF INTEREST**
None.

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