Beginning the Biomed Journey

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Autism One
May 24, 2013
Disclaimer

While Dr. Rossignol has attempted to make the information in this presentation as accurate as possible, the information is provided without any expressed or implied warranty. The purpose of this lecture is to provide information about different conditions or treatments that may affect individuals with autism and other conditions. Please be advised that Dr. Rossignol is not giving medical advice and that circumstances may dictate different treatments. All of the reviewed treatments in this lecture are considered off-label and not FDA-approved. Before beginning any treatment, please consult with your or your child’s physician.
The use of every treatment in autism is “off-label” except for Risperidone and Aripiprazole for the treatment of irritability.
Important Concept

- Several metabolic abnormalities have been reported to contribute to or cause a potentially reversible form of autism.
- The goal, from day one of evaluation, is to rapidly screen for these abnormalities and start treating them.
Although Autism Spectrum Disorders (ASD) are generally assumed to be lifelong, we review evidence that between 3% and 25% of children reportedly lose their ASD diagnosis and enter the normal range of cognitive, adaptive and social skills. Residual vulnerabilities affect higher-order communication and attention. Tics, depression and phobias are frequent residual co-morbidities after recovery.
What is Autism?

- Is classified as a disorder, not a disease
- Is a spectrum disorder
- There are no defining biomarkers
- Is diagnosed solely by behavioral observations
- Therefore, the diagnosis of autism tells us nothing about the potential causes of the disorder
What is Metabolism?

- **Definition**: set of chemical reactions that occur in living organisms to maintain life

- **Catabolism**: breaks down organic matter, for example to harvest energy in cellular respiration

- **Anabolism**: uses energy to construct components of cells such as proteins and nucleic acids
Viewing Autism as a Metabolic Disorder

- If metabolic abnormalities cause or contribute to autistic symptoms, then this implies that some of the symptoms of autism may be treatable or reversible.
- Shades of gray: not an “all or none” phenomenon [Spectrum]
  - Mitochondrial dysfunction vs. disorder
  - Epileptiform vs. epileptic activity
  - Gluten intolerance vs. celiac disease
Metabolic Abnormalities: ASD

- Mitochondrial Dysfunction
- Oxidative stress
- Impaired methylation / sulphation
- Cerebral Folate Deficiency
- Inflammation
- Seizures
- Hypothyroidism: ASD and ADHD
- Deficiencies: iron (ASD and ADHD)
Metabolic Disorders Associated with ASD

- Phenylketonuria
- Disorders of purine metabolism
- Creatine deficiency
- Biotinidase deficiency
- Cerebral folate deficiency
- SSADH deficiency
- Smith-Lemli-Opitz syndrome
- Infantile ceroid lipofuscinosis
- Histidinemia
- Ornithine transcarbamylase deficiency
- Citrullinemia
- Argininosuccinic aciduria
- Carbamoyl phosphate synthetase deficiency
- Sanfilippo syndrome

The specific role of metabolic abnormalities is largely unknown, but current research may provide insight into the pathophysiologic underpinnings of autism, at least in some patients. We review a number of known neurometabolic disorders identified as having an autistic phenotype. We also discuss the possible involvement of mitochondrial disorders and dysfunction as well as a theory regarding an increased vulnerability to oxidative stress, by which various environmental toxins produce metabolic alterations that impair normal cellular function. Finally, we review various strategies for metabolic work-up and treatment.
Choosing a Treatment

- We treat metabolic or biochemical abnormalities that may be contributing to behavior; in that sense, we are not treating “autism” or “ADHD”

- E.g., autism is treated with ABA therapy

- Use proven treatments based upon biomarkers and evidence-based medicine
Biomarkers

- **Biomarkers** help subgroup children and identify metabolic abnormalities that may be treatable
- Help to individualize treatments
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.
<table>
<thead>
<tr>
<th>Biomedical Problem</th>
<th>ASD</th>
<th>ADHD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxidative stress</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Decreased methylation and transsulfuration</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Mitochondrial dysfunction</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Metal toxicity</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Intestinal dysbiosis</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Immune dysregulation / inflammation</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Cerebral hypoperfusion</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>
Initial Screening Labs

- Mitochondrial labs
- Celiac labs (if not gluten free)
- PANDAS/PANS markers
- Methylation markers (sulfate, cysteine)
- Cholesterol
- Ferritin
- CBC, CMP
- Immune studies (IgG, IgM, IgA)
- Lead
- Magnesium
- TSH
- Vit D
- Folate receptor autoantibodies
- Brain endothelial cell autoantibodies
Cerebral Folate Deficiency
Twenty-five patients with early-onset low-functioning autism with or without neurological deficits, were evaluated for serum folate, cerebrospinal fluid (CSF) 5MTHF, and serum FR autoantibodies of the blocking type to determine the significance of folate receptor (FR) autoantibodies with respect to folate transport across the blood-CSF barrier. In spite of normal serum folate, CSF 5MTHF was low in 23 of 25 patients. The reduced CSF folate in 19 of these 23 patients could be explained by serum FR autoantibodies blocking the folate binding site of the membrane-attached FR on the choroid epithelial cells. Oral folinic acid supplements led to normal CSF 5MTHF and partial or complete clinical recovery after 12 months.
“Two patients (patients 2, 4) who were diagnosed early and received treatment were cured with full recovery from autism and neurological deficits. In the whole group these two patients were among the youngest and were detected at 2 years 8 months and at 3 years and 2 months. Three older patients (patients 11, 23, 25), diagnosed and treated from the age of 4.9, 8 and 11.9 years, did not recover from autism but showed improvement of their neurological deficits. The remaining thirteen patients in the age range of three and seven years showed a good response after treatment with improvement of most neurological deficits, but only partial recovery from their autism. The partial recovery in the latter group of 13 patients consisted of amelioration of social impairment in 4 of 13 patients, reversal of impaired communication in 9 of 13 patients and disappearance of perseverative behaviour and restricted interests in 6 of 13 patients.”

Ramaekers et al., 2007  Neuropediatrics 38(6):276-81
Folate Receptor Autoimmunity and Cerebral Folate Deficiency in Low-Functioning Autism with Neurological Deficits

Fig. 1 Changes in antibody titre and behavioural incidents over a period of six weeks in an 8.5-year-old girl with autism and neurological deficits (patient 21). The FR autoantibody titre rose from 1.2 to a maximum of 9.2 pmoles FR blocked/mL serum during this period (-■-). The increase in autoantibody titre was followed by increased incidents of aggressive behaviour (- ●-).

Ramaekers et al., 2007 Neuropediatrics 38(6):276-81
Cerebral folate deficiency is characterized by low cerebrospinal fluid (CSF) concentrations of 5-methyltetrahydrofolate and a broad spectrum of clinical signs and symptoms. A patient with progressive spasticity, gait disturbance, speech difficulties, initially diagnosed as a recessive spastic paraplegia recovered on folinic acid (15-30 mg/day) and her 5-methyltetrahydrofolate in CSF normalized. This report demonstrates the importance of CSF investigation in the diagnosis of cerebral folate deficiency and efficiency of folinic acid (5-formyltetrahydrofolate) supplementation.
Pregnancy, birth, early development were normal. At 3.5 years she presented with spasticity, gait problems, and speech difficulties. She progressively had stagnation of mental development. At age 9.5 years she had increase leg spasticity and drooling. At age 12, she started having ataxia, difficulty walking, and bladder spasticity. At age 12 years/10 months, she had a very low 5MTHF on CSF testing. She was started on 15 mg/day of folinic acid and had “an amazing effect after less than one week.” She could take a seat without falling, could negotiate stairs, was more alert, and more interested in school. By age 14 years/7 months, her gait and stability improved and her speech was near normal.

<table>
<thead>
<tr>
<th>Age</th>
<th>5MTHF (nmol/L)</th>
<th>5HIAA (nmol/L)</th>
<th>HVA (nmol/L)</th>
<th>Neo (nmol/L)</th>
<th>Bio (nmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>12 years 11 months (before treatment)</td>
<td>34.4</td>
<td>93</td>
<td>174</td>
<td>14.8</td>
<td>12.1</td>
</tr>
<tr>
<td>13 years 2 months (on treatment with folinic acid 15 mg/day)</td>
<td>127.1</td>
<td>154</td>
<td>293</td>
<td>11.6</td>
<td>12.6</td>
</tr>
<tr>
<td>Controls (10–16 years) n = 137 Median (5–95. perc.)</td>
<td>67.0</td>
<td>138.0</td>
<td>305.0</td>
<td>13.0</td>
<td>18.0</td>
</tr>
<tr>
<td></td>
<td>42.0–119.6</td>
<td>71.8–231.8</td>
<td>146.3–533.2</td>
<td>8.0–23.0</td>
<td>10.9–32.0</td>
</tr>
</tbody>
</table>

The prevalence of MD in the general population of ASD was 5.0% (95% confidence interval 3.2, 6.9%), much higher than found in the general population (approximately 0.01%). The prevalence of abnormal biomarker values of mitochondrial dysfunction was high in ASD, much higher than the prevalence of MD. Taken together, these findings suggest children with ASD have a spectrum of mitochondrial dysfunction of differing severity. Eighteen publications representing a total of 112 children with ASD and MD (ASD/MD) were identified. The prevalence of developmental regression (52%), seizures (41%), motor delay (51%), gastrointestinal abnormalities (74%), female gender (39%), and elevated lactate (78%) and pyruvate (45%) was significantly higher in ASD/MD compared with the general ASD population. 53% of children with ASD/MD had a complex I deficiency.
We observed significantly lower levels of complexes III and V in the cerebellum ($p < 0.05$), of complex I in the frontal cortex ($p < 0.05$), and of complexes II ($p < 0.01$), III ($p < 0.01$), and V ($p < 0.05$) in the temporal cortex of children with autism as compared to age-matched control subjects, while none of the five ETC complexes was affected in the parietal and occipital cortices in subjects with autism. A significant increase in the levels of lipid hydroperoxides, an oxidative stress marker, was also observed in the cerebellum and temporal cortex in the children with autism.
Labs: MtD (blood)

- Elevated lactic acid and pyruvate
- Elevated ammonia (>40 µg/dL)
- Low carnitine, free and total
- Elevated creatine kinase (>150 U/L)
- Fasting plasma amino acids: alanine (>450 µmol/L); alanine/lysine (>2.5)
- Fasting plasma acylcarnitine analysis (3 or more elevations)
- AST/ALT > 2.0
# Treatments for mitochondrial dysfunction associated with PDH mutations

<table>
<thead>
<tr>
<th>Vitamin</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Electron Transport Chain Support</strong></td>
<td></td>
</tr>
<tr>
<td>Co-enzyme Q10: Ubiquinol</td>
<td>5–30 mg/kg/day divided in 2 doses per day</td>
</tr>
<tr>
<td>Co-enzyme Q10: Ubiquinone</td>
<td>10–30 mg/kg/day divided in 2 doses per day</td>
</tr>
<tr>
<td><strong>Energy Storage and Transportation</strong></td>
<td></td>
</tr>
<tr>
<td>Creatine monohydrate</td>
<td>0.1 g/kg/day divided in 1–2 doses per day</td>
</tr>
<tr>
<td><strong>Fatty Acid Oxidation Support</strong></td>
<td></td>
</tr>
<tr>
<td>L-carnitine</td>
<td>30–100 mg/kg/day divided in 2–3 doses per day</td>
</tr>
<tr>
<td>Acetyl-L-carnitine</td>
<td>250–1000 mg/day divided in 2 doses per day</td>
</tr>
<tr>
<td>Biotin (B7)</td>
<td>5–10 mg/day given once per day</td>
</tr>
<tr>
<td><strong>B-Vitamins</strong></td>
<td></td>
</tr>
<tr>
<td>Thiamine (B1)</td>
<td>50–100 mg/day given once per day</td>
</tr>
<tr>
<td>Riboflavin (B2)</td>
<td>100–400 mg/day given once per day</td>
</tr>
<tr>
<td>Niacin (B3)</td>
<td>50–100 mg/day given once per day</td>
</tr>
<tr>
<td>Pyridoxine (B6)</td>
<td>200 mg/day given once per day</td>
</tr>
<tr>
<td><strong>Antioxidants</strong></td>
<td></td>
</tr>
<tr>
<td>Acetyl-L-carnitine</td>
<td>250–1000 mg/day divided in 2 doses per day</td>
</tr>
<tr>
<td>Vitamin E</td>
<td>200–400 IU/day given once per day</td>
</tr>
<tr>
<td>Vitamin C</td>
<td>100–500 mg/day given once per day</td>
</tr>
<tr>
<td>alpha-lipoic acid</td>
<td>50–200 mg/day given once per day</td>
</tr>
<tr>
<td><strong>Oxidative Stress Support</strong></td>
<td></td>
</tr>
<tr>
<td>Methylcobalamin (B12)</td>
<td>5–1000 mcg/day given once per day</td>
</tr>
<tr>
<td>Folinic Acid / leucovorin (B9)</td>
<td>400–800 ug/day given once per day</td>
</tr>
<tr>
<td>5-methyltetrahydrofolate (B9)</td>
<td>400–800 ug/day given once per day</td>
</tr>
<tr>
<td>N-acetyl-L-cysteine (NAC)</td>
<td>10–70 mg/kg/day divided in 1–3 doses</td>
</tr>
</tbody>
</table>
Oxidative Stress
Oxidative Stress

Oxygen

8 electrons → 1 electron ejected → 7 electrons

Free Radical
Respiratory Chain

\[ \text{O}_2 \rightarrow \text{SOD} \rightarrow \text{H}_2\text{O}_2 \rightarrow \text{Catalase} \rightarrow \text{H}_2\text{O} \]

\[ \text{OH} \rightarrow \text{mtDNA} \]

Mitochondrial Permeability Transition

Lipid Peroxidation
Antioxidant

Oxygen

8 electrons
Oxidative stress found in brain areas that are associated with the speech processing, sensory and motor coordination, emotional and social behavior, and memory.
Antioxidant Treatment: Suggested Doses

- Vitamin C: 100 mg/kg/day
- Coenzyme Q 10: 5-10 mg/kg/day
- Acetyl-L-Carnitine: 50-100 mg/kg/day
- L-Carnosine: 200-400 mg twice a day
- Pycnogenol: 1 mg/kg/day (often higher)
- MB12 injections: 75 mcg/kg every 1-3 days
- Folinic acid: 400 mcg twice a day
- Omega-3’s: DHA and EPA ~800 mg/day each
- Zinc 20-100 mg/day
- Melatonin: 1-3 mg 30 mins before bedtime
Impaired Methylation and Sulphation
SAMe
Cysteine
Glutathione
MB12 active
SAH
Homocysteine
Methionine Cycle
Folic Acid
Methyl Folate
Oral B12 inactive
MB12 active
Folate Cycle
MTHFR
Oral B12
inactive
MB12 active
Trans-sulfuration Pathway
Cysteine
Glutathione
Detoxification
Toxic Metals
Free Radicals
Biliary mercury secretion is tied to glutathione secretion

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. Plasma levels of cysteine, glutathione, and the ratio of reduced to oxidized glutathione, an indication of antioxidant capacity and redox homeostasis, were significantly decreased. We propose that an increased vulnerability to oxidative stress (endogenous or environmental) may contribute to the development and clinical manifestations of autism.

James et al., 2006  Am J Med Genetics Part B 141B:947-56
Based on reports of abnormal methionine and glutathione metabolism in autistic children, it was of interest to examine the same metabolic profile in the parents. The results indicated that parents share similar metabolic deficits in methylation capacity and glutathione-dependent antioxidant/detoxification capacity observed in many autistic children.

James et al., 2008  J Autism Dev Disord 38(10):1966-75
The aim of this randomized, double-blind, placebo-controlled trial was to investigate the influence of administered Pycnogenol or placebo on the level of reduced (GSH) and oxidized (GSSG) glutathione in children suffering from ADHD. One month of Pycnogenol administration (1 mg/kg/day) caused a significant decrease in GSSG and a highly significant increase in GSH levels as well as improvement of GSH/GSSG ratio in comparison to a group of patients taking a placebo.
In an open-label trial, 40 autistic children were treated with 75 mcg/kg methylcobalamin (2 times/wk) and 400 mcg folinic acid (bid) for 3 mo. The 3-mo intervention resulted in significant increases in cysteine, cysteinylglycine, and glutathione concentrations (P < 0.001). Measures of autistic behavior were assessed by a trained study nurse before and after treatment using the Vineland Adaptive Behavior Scales. Although significant improvement was observed after treatment, the scores remained significantly below standard normal scores.
Increasing Glutathione

- Antioxidants
- Pycnogenol
- Methylcobalamin injections
- Folinic acid 400 mcg twice a day
- Glutathione
- NAC (N-acetylcysteine)
- Vitamins C and E
Cholesterol Deficiency
In the Third National Health and Nutrition Examination Survey (1988-1994), serum total cholesterol was measured in 4,852 children aged 6-16 years. Non-African-American children with a serum total cholesterol concentration below the 25th percentile (<145 mg/dl) were almost threefold more likely to have been suspended or expelled from schools than their peers with total cholesterol at or above the 25th percentile (odds ratio = 2.96, 95% confidence interval: 1.55, 5.64).
Children receiving cholesterol treatment display fewer autistic behaviours, infections, and symptoms of irritability and hyperactivity, with improvements in physical growth, sleep and social interactions. Other behaviours shown to improve with cholesterol supplementation include aggressive behaviours, self-injury, temper outbursts and trichotillomania.

Aneja and Tierney, 2008  Int Rev Psychiatry 20(2):165-70
Iron Deficiency
This study confirmed a much higher prevalence of iron deficiency in children with ASD than in the general population. This may be associated with more severe ASD impairment. The high rate of microcytosis supports the presence of iron deficiency, but its associated high prevalence of ferritin above cutoff values suggests that ferritin measurements may miss some children with iron deficiency and supports the need for multiple markers. In conclusion, children with ASD represent a high risk group for iron deficiency, and need close monitoring, even at school-age.
At baseline and post-treatment visits, parents completed a Sleep Disturbance Scale for Children and a Food Record. Seventy-seven percent had restless sleep at baseline, which improved significantly with iron therapy, suggesting a relationship between sleep disturbance and iron deficiency in children with autism spectrum disorder. Similar prevalence of low ferritin at school age as preschool age indicates that children with autism spectrum disorder require ongoing screening for iron deficiency.
Twenty-three nonanemic children (aged 5-8 years) with serum ferritin levels <30 ng/mL who met DSM-IV criteria for ADHD were randomized (3:1 ratio) to either oral iron (ferrous sulfate, 80 mg/day, n = 18) or placebo (n = 5) for 12 weeks. Iron supplementation (80 mg/day) appeared to improve ADHD symptoms in children with low serum ferritin levels. Iron therapy was well tolerated and effectiveness is comparable to stimulants.
Sleep Problems
Sleep problems are frequently reported by parents of children with autism with prevalence estimates of 44-83% for sleep disorders in this population. To better understand sleep in autism, we surveyed sleep problems in 210 children with autism using a Likert-based questionnaire for parent report. The most frequently reported sleep problems included difficulty in falling asleep, restless sleep, not falling asleep in own bed, and frequent wakenings. An association was noted between certain medical problems and sleep problems.
## Table 2: Sleep problems frequency

<table>
<thead>
<tr>
<th>Sleep problem*</th>
<th>Percentage of parents reporting</th>
</tr>
</thead>
<tbody>
<tr>
<td>Difficulty falling asleep</td>
<td>53.3</td>
</tr>
<tr>
<td>Restless sleep</td>
<td>40</td>
</tr>
<tr>
<td>Unwillingness to fall asleep in own bed</td>
<td>39.5</td>
</tr>
<tr>
<td>Frequent wakenings</td>
<td>33.8</td>
</tr>
<tr>
<td>Difficulty arousing</td>
<td>31.5</td>
</tr>
<tr>
<td>Enuresis</td>
<td>27.7</td>
</tr>
<tr>
<td>Disoriented waking</td>
<td>27.1</td>
</tr>
<tr>
<td>Daytime mouth breathing</td>
<td>25.7</td>
</tr>
<tr>
<td>Excessive daytime sleepiness</td>
<td>23.3</td>
</tr>
<tr>
<td>Bruxism</td>
<td>21</td>
</tr>
<tr>
<td>Snoring</td>
<td>21</td>
</tr>
<tr>
<td>Fear of sleeping in dark</td>
<td>18.6</td>
</tr>
<tr>
<td>Awakens to noise</td>
<td>18%</td>
</tr>
<tr>
<td>Vocalizes in sleep</td>
<td>10.5</td>
</tr>
<tr>
<td>Breathing concerns</td>
<td>8.6</td>
</tr>
<tr>
<td>Headbanging</td>
<td>6.7</td>
</tr>
<tr>
<td>Gets up to go to bathroom during night</td>
<td>6.2</td>
</tr>
<tr>
<td>Wakes up screaming</td>
<td>5.2</td>
</tr>
<tr>
<td>Falls asleep at school</td>
<td>4.7</td>
</tr>
<tr>
<td>Nightmares</td>
<td>3.8</td>
</tr>
<tr>
<td>Apnea</td>
<td>3.4</td>
</tr>
<tr>
<td>Cries during night</td>
<td>1.9</td>
</tr>
<tr>
<td>Morning headaches</td>
<td>1</td>
</tr>
<tr>
<td>Sleepwalking</td>
<td>1</td>
</tr>
</tbody>
</table>

*Based on parent reports of problem occurring ‘frequently’ or ‘almost always’.
Treatments for Sleep Problems in ASD

- Multivitamin
- L-Carnitine (Rett syndrome)
- Melatonin
- 5-HTP
- Dietary changes
- Medications
- Treatment of sleep apnea
Melatonin in Autism

Melatonin: 6 randomized, double-blind, placebo-controlled studies have demonstrated improvements in the amount of time to fall asleep, number of nighttime awakenings, and/or length of sleep compared to both baseline and/or to placebo.

- Garstang and Wallis, 2006 Child Care Health Dev 32(5):585-9
- Wasdell et al., 2008 J Pineal Res 44:57-64
- Wirojanan et al., 2009 J Clin Sleep Med 5:145-50
- Wright et al., 2011 J Autism Dev Disord 41(2):175-84
- Cortesi et al., 2012 J Sleep Res, in press
Randomized controlled trial of melatonin for children with autistic spectrum disorders and sleep problems

Garstang and Wallis, 2006  Child Care Health Dev 32(5):585-9
GI Problems in ASD
Gastrointestinal symptoms (assessed by the 6-GSI) were strongly correlated with the severity of autism (assessed by the ATEC), \( r=0.59, p<0.001 \). Children with 6-GSI scores above 3 had much higher ATEC Total scores than those with 6-GSI-scores of 3 or lower \( (81.5 +/- 28 \text{ vs. 49.0 +/- 21, } p=0.00002) \). Children with autism had lower levels of species of Bifidobacter (-43%, \( p=0.002 \)) and higher levels of species of Lactobacillus (+100%, \( p=0.00002 \)), but similar levels of other bacteria and yeast using standard culture growth-based techniques. The strong correlation of gastrointestinal symptoms with autism severity indicates that children with more severe autism are likely to have more severe gastrointestinal symptoms and vice versa. 

Adams et al., 2011 BMC Gastroenterol 11(1):22
Intestinal disaccharidase activities were measured in 199 individuals with autism to determine the frequency of enzyme deficiency. All patients had duodenal biopsies that were evaluated morphologically and assayed for lactase, sucrase, and maltase activity. Frequency of lactase deficiency was 58% in autistic children ≤ 5 years old and 65% in older patients. As would be expected, patients with autism at age 5 > years demonstrated significant decline in lactase activity (24%, p = .02) in comparison with ≤ 5 years old autistic patients. Lactase deficiency not associated with intestinal inflammation or injury is common in autistic children and may contribute to abdominal discomfort, pain and observed aberrant behavior. Most autistic children with lactose intolerance are not identified by clinical history.
A case is presented of a 5-year old boy diagnosed with severe autism at a specialty clinic for autistic spectrum disorders. After initial investigation suggested underlying celiac disease and varied nutrient deficiencies, a gluten-free diet was instituted along with dietary and supplemental measures to secure nutritional sufficiency. The patient’s gastrointestinal symptoms rapidly resolved, and signs and symptoms suggestive of autism progressively abated. This case is an example of a common malabsorption syndrome associated with central nervous system dysfunction and suggests that in some contexts, nutritional deficiency may be a determinant of developmental delay. It is recommended that all children with neurodevelopmental problems be assessed for nutritional deficiency and malabsorption syndromes.

Genuis and Bouchard, 2010  J Child Neurol, in press
Moderate or severe constipation was more frequent in the autistic group than in the control subjects (36% vs 10%). Analysis of rectosigmoid loading showed more striking differences (54.4% of autistic children had moderate/severe loading or acquired megarectum compared with 24.1% of control subjects). Multivariate regression analysis showed consumption of milk to be the strongest predictor of constipation in the autistic group.

CONCLUSIONS: Constipation is a frequent finding in children with gastrointestinal symptoms and autism, particularly in the rectosigmoid colon, often with acquired megarectum.
Dietary Changes
The effect of particular foods on levels of hyperactivity, uncontrolled laughter, and disruptive behaviors was studied in an 8-year-old autistic boy. The floor of the child's room was taped off into 6 equal-sized rectangles to measure general activity level. Frequency data were recorded on screaming, biting, scratching, and object throwing. During an initial 4-day period the child was fed a normal American diet. A 6-day fasting period followed, during which time only spring water was allowed. The third phase lasted 18 days and involved the presentation of individual foods. During the final phase the child was given only foods that had not provoked a reaction in the third phase. Results showed that foods such as wheat, corn, tomatoes, sugar, mushrooms, and dairy products were instrumental in producing behavioral disorders with this child.

We report results from a two-stage, 24-month, randomised controlled trial incorporating an adaptive ‘catch-up’ design and interim analysis. Based on per protocol repeated measures analysis, data for 26 diet children and 29 controls were available at 12 months. At this point, there was a significant improvement to mean diet group scores (time–treatment interaction) on sub-domains of ADOS, GARS and ADHD-IV measures. Our results suggest that dietary intervention may positively affect developmental outcome for some children diagnosed with ASD.

Whiteley et al., 2010  Nutrit Neuroscience 13(2), in press
A milk-free diet downregulates folate receptor autoimmunity in cerebral folate deficiency syndrome

Ramaekers et al., 2008  Dev Med Child Neurol 50(5):346-52
DIAGNOSIS AUTISM: NOW WHAT?
A SIMPLIFIED BIOMEDICAL APPROACH

By Dan Rossignol, MD, FAAFP
Novel and emerging treatments for autism spectrum disorders: A systematic review

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.
### TABLE 7

**Summary of treatments and their effects on certain autistic behaviors**

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<tr>
<th>Speech/communication</th>
<th>Carnitine</th>
<th>Carnosine</th>
<th>GFCF diet</th>
<th>Alpha-2 adrenergic agonists</th>
<th>Cyproheptadine</th>
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AI: Acetylcholinesterase inhibitors; AIT: auditory integration training;
GFCF: gluten-free, casein-free diet; HBOT: hyperbaric oxygen treatment;