Metabolic Abnormalities in Autism: Analysis and New Treatments

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Disability

While Dr. Rossignol has attempted to make the information in this presentation as accurate as possible, the information is provided without any express or implied warranty. The purpose of this lecture is to provide information about different conditions or treatments that 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. If the issues that are discussed in this lecture affect you or your loved ones, seek professional advice. 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.

Autism Spectrum

Asperger Syndrome PDD-NOS Autistic Disorder

Psychologically / Behaviorally defined

Communication

Stereotypical behaviors

Social interaction

Underlying pathophysiology (biomedical problems): ???

Autisms

• There are many types of autism and thus multiple subgroups
• There are probably many causes of autism
• Biomarkers will help subgroup children and identify metabolic abnormalities that may be treatable

Genetics

• Genetic syndromes only account for an estimated 6-15% of autism
• Genetics do not account for epigenetics – e.g., DNA methylation
• Genetics also do not account for environmental factors

Biomarker-Guided Interventions of Clinically Relevant Conditions Associated with Autism Spectrum Disorders and Attention Deficit Hyperactivity Disorder

James Jeffrey Braddock, MD, MDCH; FAAFP; Scott Smalls, PA; Matthew Bovd, ND; Daniel A. Rossignol, MD, FAAFP

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.

**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

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**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
  - Mitochondrial dysfunction vs. disorder
  - Epileptiform vs. epileptic activity
  - Gluten intolerance vs. celiac disease

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**Examples: Metabolic problems**

- **Inhibitory substances**
  - Toxins
  - Propionic acid
  - Abnormal antibodies (e.g., folate receptor)
- **Deficiencies**
  - Glutathione (GSH)
  - Antioxidants
  - Antioxidant enzymes
  - Iron

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**Behaviors Associated With Fever in Children With Autism Spectrum Disorders**

In this prospective study of 30 children with ASD, fever greater than 100.4°F was associated with a transient decrease in irritability, hyperactivity, stereotypy, and inappropriate speech as reported on the Aberrant Behavior Checklist (ABC) compared to 30 control ASD children without fever. Twenty-five of 30 (83%) children had an improvement in at least one domain.

Curran et al., 2007 Pediatrics 120(6):e1386-92

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**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

**Metabolic abnormalities: ASD**

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

**Oxidative Stress**

Oxidative stress found in brain areas that are associated with the speech processing, sensory and motor coordination, emotional and social behavior, and memory.

Sajdel-Sulkowska et al., 2010. Cerebellum, in press
Recent research has indicated a possible role of abnormalities in oxidative homeostasis in the pathophysiology of autism, based on reports that a range of oxidative biomarkers are significantly altered in people with autism. This article reviews the current findings on oxidative stress in autism, including genetic links to oxidative pathways, changes in antioxidant levels and other oxidative stress markers. Take home message: Abnormalities in oxidative homeostasis may play a role in the pathophysiology of autism. Antioxidant treatment may form a potential therapeutic pathway for this complex disorder.

Testing: Oxidative Stress

- Urinary 8-OHDG
- Urinary 8-OHG
- Urinary Isoprostanes
- Cysteine
- Glutathione

Table 1

<table>
<thead>
<tr>
<th>Antioxidant</th>
<th>Dose (based on studies reviewed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin C</td>
<td>1000 mg/kg/day</td>
</tr>
<tr>
<td>Acetyl L carnitine</td>
<td>100 mg/kg/day</td>
</tr>
<tr>
<td>L-carnitine</td>
<td>100 mg/kg/day and approx. 1600 mg/day</td>
</tr>
<tr>
<td>4-Hydroxypropiol</td>
<td>1-2 mg/kg/day</td>
</tr>
<tr>
<td>Methylcobalamin</td>
<td>75 mcg/kg/day and 4-6 times per week</td>
</tr>
<tr>
<td>Folic acid</td>
<td>400 mcg twice a day</td>
</tr>
<tr>
<td>Vitamin B12</td>
<td>oral B12 inactive: approx. 500 mcg/day</td>
</tr>
<tr>
<td>Methyl folate</td>
<td>approx. 1000 mg/day and approx. 1600 mg/day</td>
</tr>
<tr>
<td>DNA</td>
<td>700-1000 mg/day</td>
</tr>
<tr>
<td>Methionine</td>
<td>1-3 mg, 30 minutes before bedtime</td>
</tr>
<tr>
<td>Magnesium</td>
<td>30 mg/kg/day</td>
</tr>
<tr>
<td>Vitamin B6</td>
<td>0.6 mg/kg/day</td>
</tr>
</tbody>
</table>

Impaired Methylation and Sulphation

- MTHFR
- Methyl Folate
- SAMe
- Methionine Cycle
- Folate Cycle
- Detoxification
- Toxic Metals
- Free Radicals
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 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.

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.

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.

The aim of this randomized, double-blind, placebo-controlled trial was to investigate the influence of administered Pycnogenol or placebo on the level of glutathione in children suffering from attention deficit hyperactivity disorder (ADHD). One month of Pycnogenol administration (1 mg/kg/day) caused a significant decrease in GSH 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.

Increasing Glutathione

- Antioxidants
- Pycnogenol
- Methylcobalamin injections
- Folinic acid 400 mcg twice a day
- Glutathione
- NAC (N-acetylcysteine)
- Vitamins C and E
- [Magnesium sulfate]

Inflammation
Two independent studies have described bilateral temporal hypoperfusion in autistic children. Significant negative correlation was observed between cerebral blood flow (rCBF) and Autism Diagnostic Interview-Revised (ADI-R) score in the left superior temporal gyrus. The more severe the autistic syndrome, the more rCBF is low in this region, suggesting that left superior temporal hypoperfusion is related to autistic behavior severity.

<table>
<thead>
<tr>
<th>Area of Hypoperfusion</th>
<th>Clinical Correlation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thalamus</td>
<td>Repetitive, self-stimulatory, and unusual behaviors [Starkstein, 2000]</td>
</tr>
<tr>
<td>Temporal lobes</td>
<td>Desire for sameness and social/communication impairments [Ohnishi, 2000]</td>
</tr>
<tr>
<td>Temporal lobes and amygdala</td>
<td>Impairments in processing facial expressions/emotions [Critchley, 2000]</td>
</tr>
<tr>
<td>Fusiform gyrus</td>
<td>Difficulty recognizing familiar faces [Pierce, 2004]</td>
</tr>
<tr>
<td>Wernicke’s and Brodmann’s areas</td>
<td>Decreased language development and auditory processing problems [Wilcox, 2002; Böddiart, 2002]</td>
</tr>
<tr>
<td>Temporal and Frontal lobes</td>
<td>Decreased IQ [Hashimoto, 2000]</td>
</tr>
</tbody>
</table>

Hypoperfusion of the prefrontal and left temporal areas worsened and became "quite profound" as the age of the child increased.

Wilcox et al., 2002 Neuropsychobiology 46(1):13-6
Elevation of Tumor Necrosis Factor-Alpha in Cerebrospinal Fluid of Autistic Children

<table>
<thead>
<tr>
<th>Patient</th>
<th>Treatment</th>
<th>CSF (pg/mL)</th>
<th>Serum (pg/mL)</th>
<th>CSF/Serum Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>No</td>
<td>124</td>
<td>1.6</td>
<td>73.5</td>
</tr>
<tr>
<td>2</td>
<td>No</td>
<td>140</td>
<td>2.0</td>
<td>70.0</td>
</tr>
<tr>
<td>3</td>
<td>No</td>
<td>181</td>
<td>8.2</td>
<td>22.3</td>
</tr>
<tr>
<td>4</td>
<td>No</td>
<td>16</td>
<td>2.1</td>
<td>7.6</td>
</tr>
<tr>
<td>5</td>
<td>No</td>
<td>185</td>
<td>2.7</td>
<td>57.4</td>
</tr>
<tr>
<td>6</td>
<td>No</td>
<td>385</td>
<td>1.4</td>
<td>275</td>
</tr>
<tr>
<td>7</td>
<td>Yes</td>
<td>12</td>
<td>1.7</td>
<td>7.1</td>
</tr>
<tr>
<td>8</td>
<td>Yes</td>
<td>13</td>
<td>1.5</td>
<td>9.9</td>
</tr>
<tr>
<td>9</td>
<td>Yes</td>
<td>11</td>
<td>1.5</td>
<td>8.5</td>
</tr>
<tr>
<td>10</td>
<td>Yes</td>
<td>13</td>
<td>2.5</td>
<td>5.7</td>
</tr>
</tbody>
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Ming et al., 2005  Prostaglandins Leukot Essent Fatty Acids 73(5):379-84

Inflammation: Testing

Urinary levels of neopterin and bioprotein in autism

Table 1

<table>
<thead>
<tr>
<th>Neopterin (µmol/mol creatinine)</th>
<th>Bioprotein (µmol/mol creatinine)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autistic children (n = 14)</td>
<td>3.11 ± 0.88**</td>
</tr>
<tr>
<td>Siblings (n = 21)</td>
<td>1.49 ± 0.46</td>
</tr>
<tr>
<td>Control children (n = 16)</td>
<td>2.93 ± 0.26**</td>
</tr>
</tbody>
</table>

Data are the mean ± S.E.M. Significantly different from controls: *P < 0.01, **P < 0.001.

Messahel et al., 1998  Neurosci Letters 241:17-20

Increased excretion of a lipid peroxidation biomarker in autism

Ming et al., 2005  Prostaglandins Leukot Essent Fatty Acids 73(5):379-84

Membrane Oxidative Damage

Urinary Isoprostane F2-alpha

Increased oxidative stress damage
Other tests

- C-reactive protein / Sed rate
- Platelet count
- GI: fecal calprotectin / lactoferrin
- Inflammatory comorbidities:
  - Eczema
  - Asthma
  - Allergies

Treatments: Inflammation

- Diet
  - Remove foods causing immune stimulation; avoid toxins; well-balanced diet
- Supplements to support metabolism
  - Omega-3 fatty acids
  - Vitamins
  - Minerals
  - Antioxidants
  - Probiotics
- Anti-inflammatory medications
- HBOT

Case Study: Corticosteroid Treatment of Language Regression in Pervasive Developmental Disorder

The authors describe a child whose language and behavior regressed at 22 months and in whom pervasive developmental disorder was later diagnosed. At 6 years, he displayed a profound receptive-expressive aphasia accompanied by behavioral disturbances characterized by hyperactivity, impaired social interactions, tantrums, gestural stereotypes, and echolalia. Corticosteroid treatment resulted in amelioration of language abilities and behavior.

Stefanatos et al., 1995  J Am Acad Child Adolesc Psychiatry 34(8):1107-11

Response to steroid therapy in autism secondary to autoimmune lymphoproliferative syndrome

Previously developmentally normal, he had symptoms of autism with rapid regression in developmental milestones coincident with the onset of lymphoproliferation and autoimmune hemolytic anemia. Low-dose steroid therapy induced early and complete remission in the ALPS phenotype. There was subjective improvement, followed by objective improvement in speech and developmental milestones. We propose that autism may be part of the autoimmune disease spectrum of ALPS in this child.

A total of 25 children (average age 7.9 ±0.7 year old) were enrolled. Safety was assessed by measurements of metabolic profiles and blood pressure. There were no adverse effects noted and behavioral measurements revealed a significant decrease in 4 out of 5 subcategories (irritability, lethargy, stereotypy, and hyperactivity). Improved behaviors were inversely correlated with patient age, indicating stronger effects on the younger patients.

Heuer et al., 2008 Autism Res 1(5):275-283
Children with autism have a significantly reduced level of plasma IgG (5.39+/0.29 mg/mL) compared to the TD (7.72+/0.28 mg/mL; P<0.001) and DD children (8.23+/0.49 mg/mL; P<0.001). Children with autism also had a reduced level of plasma IgM (0.670.06 mg/mL) compared to TD (0.79+/0.05 mg/mL; P<0.05). Ig levels were negatively correlated with ABC scores for all children (IgG: r=-0.334, P<0.0001; IgM: r=-0.167, P=0.0285).

Bradstreet et al., 2007 Med Hypotheses 68(5):979-87
Reduced Levels of Immunoglobulin in Children With Autism Correlates With Behavioral Symptoms

Bradstreet et al., 2007 Med Hypotheses 68(5):979-87
Spironolactone might be a desirable immunologic and hormonal intervention in autism spectrum disorders

Gupta et al., 2010 J Clin Immunol
Accumulating data including changes in immune responses, linkage to major histocompatibility complex antigens, and the presence of autoantibodies to neural tissues/antigens suggest that the immune system plays an important role in its pathogenesis. In this brief review, we discuss the data regarding changes in both innate and adaptive immunity in autism and the evidence in favor of the role of the immune system, especially of maternal autoantibodies in the pathogenesis of a subset of patients with autism. The rationale for possible therapeutic use of intravenous immunoglobulin is also discussed.

Heuer et al., 2008 Autism Res 1(5):275-283
Adaptive and Innate Immune Responses in Autism: Rationale for Therapeutic Use of Intravenous Immunoglobulin

Bradstreet et al., 2007 Med Hypotheses 68(5):979-87
Spironolactone might be a desirable immunologic and hormonal intervention in autism spectrum disorders

Boris et al., 2007 J Neuroinflammation 4:3

In documented autistic children, 400mg/kg IVIG was administered each month for 6 months. Baseline and monthly Aberrant Behavior Checklists were completed on each child in order to measure the child’s response to IVIG. The participants’ overall aberrant behaviors decreased substantially soon after receiving their first dose of IVIG. Further analysis of the total scores revealed decreases in hyperactivity, inappropriate speech, irritability, lethargy and stereotypy. However, 22 of the 26 children regressed to their pre-IVIG status within 2–4 months of discontinuing the IVIG.


Improvement in children with autism treated with intravenous gamma globulin

Boris et al., 2006 J Neuroinflammation 4:3

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Table 2. Summary of the proposed effects of spironolactone on autism findings

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<td>Interferon gamma</td>
<td>↑ [19]</td>
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<td>TNF-α</td>
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* Dierickx et al. in a subset of autistic individuals.

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* Dierickx et al. in a subset of autistic individuals.
Naltrexone increased T-helper cells and decreased T-suppressor cells in children with autism. Naltrexone given at doses of 0.5, 1.0 and 1.5 mg/kg every 48 hours.

Anti-inflammatories: Typical doses
- Prednisone: 1-2 mg/kg/day tapered unless using higher-dose protocol
- Spironolactone: 2-3 mg/kg/day target
- Actos: 15-60 mg/day
- Singulair: 4-10 mg/day
- Minocycline: 50-100 mg bid
- IVIG: 400-800 mg/kg once a month (unless treating PANDAS)

Seizures: Definition
- Episodes of disturbed brain function that cause changes in attention or behavior
- Caused by abnormally excited electrical signals that disrupt the smooth-running pattern of electrical activity in the brain causing overload
- Epilepsy: recurrent seizures

Seizures: Symptoms
- Subclinical (silent)
- Staring spells
- Rapid blinking, holding of the hands to the ears, unprovoked crying episodes
- Loss of consciousness
- Violent convulsions
- Aura: strange sensation (such as tingling, emotional change, or smell of odor not there)
Absence Seizure

Seizures in Autism
- Prevalence ranges from 8-42%, with most estimates at 25-30%
- Prevalence of EEG epileptiform activity approaches 60%

Frequency of epileptiform EEG abnormalities in a sequential screening of autistic patients with no known clinical epilepsy from 1996 to 2005

This retrospective review of 24-hour ambulatory digital EEG data collected from 889 ASD patients presenting between 1996 and 2005 shows that 540 of 889 (60.7%) subjects had abnormal EEG epileptiform activity in sleep with no difference based on clinical regression. The most frequent sites of epileptiform abnormalities were localized over the right temporal region. Of 176 patients treated with valproic acid, 80 normalized on EEG and 30 more showed EEG improvement compared with the first EEG (average of 10.1 months to repeat EEG).

Chez et al., 2006 Epilepsy Behav 8(1):267-71

Magnetocorelephographic Patterns of Epileptiform Activity in Children With Regressive Autism Spectrum Disorders

Lewine et al., 1999 Pediatrics 104:405-18

SLEEP DISORDERS, EPILEPSY, AND AUTISM

Studies are presented to support the view that sleep is abnormal in individuals with autistic spectrum disorders. Epilepsy and sleep have reciprocal relationships, with sleep facilitating seizures and seizures adversely affecting sleep architecture. The hypothesis put forth is that identifying and treating sleep disorders, which are potentially caused by or contributed to by autism, may impact favorably on seizure control and on daytime behavior.


Seizure: Treatments
- Nutritional supplements
- Medications
- Steroids / IVIG
- Diet (ketogenic)
- HBOT
- Vagal nerve stimulator
- Surgery
Supplements with Antiseizure Activity

- Melatonin
- Taurine
- Vitamin B6 / P5P
- Magnesium
- Omega-3 fatty acids
- GABA
- DMG
- L-Carnosine
- Folinic acid

Treatments

- We treat metabolic or biochemical abnormalities that may be contributing to autistic behavior; in that sense, we are not treating “autism”
- Treatments either work or do not work; there really is no such thing as an “alternative” treatment
- Use proven treatments based upon evidence-based medicine
- Treatments based on symptoms or labs

Treat Underlying Contributor(s)

Example: ADHD

- Cause / Contributor: ?
- Treatment: stimulants
- Possible contributors: low iron, omega-3 fatty acid deficiency, lead or pesticide exposure, low glutathione, oxidative stress
- Potential treatments: supplements (zinc, iron, pycnogenol, omega 3’s, carnitine, galantamine), nutrition, detox, then perhaps stimulants

Treatment: Paradigm Shift

Drug-first Viewpoint

- Viewing autism as a fixed disorder where symptoms are treated with medication(s); underlying causes not typically investigated
- Example: Risperidone to treat aggression or irritability
- Goal: Control symptoms, recovery not possible

Underlying Contributor Viewpoint

- Viewing autism as a dynamic disorder with underlying contributions from oxidative stress, mitochondrial dysfunction, inflammation, etc... and treating these problems, reserving meds for less responsive cases
- Goal: Improve symptoms, recovery possible


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 carnitine, multivitamin/mineral complex, piracetam, polyunsaturated fatty acids, vitamin B6/magnesium, elimination diets, chelation, cyproheptadine, famotidine, glutamate antagonists, acupuncture, auditory integration training, massage, and neurofeedback.