Metabolic Abnormalities in Autism: Analysis and New Treatments

Dan Rossignol, MD FAAFP
International Child Development Resource Center
321-259-7111 www.icdrc.org
rossignolmd@gmail.com

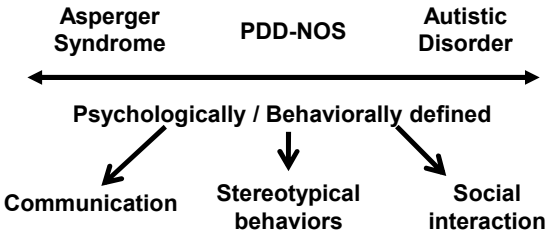
www.danrossignolmd.com

Autism One Conference
May 29, 2011

Disclaimer

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



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

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

James Jeffrey Bradstreet, MD, MD(H), FAAFP; Scott Smith, PA; Matthew Baral, 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.

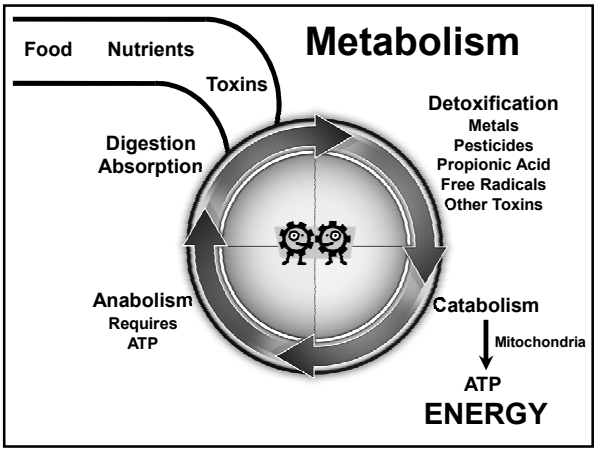
Bradstreet et al., 2010 Altern Med Rev 15(1):15-32

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

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



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

Behaviors Associated With Fever in Children With Autism Spectrum Disorders

Laura K. Curran, PhD[a,b], Craig J. Newschaffer, PhD[c], Li-Ching Lee, PhD[a], Stephen O. Crawford, MHS[a], Michael V. Johnston, MD[b], Andrew W. Zimmerman, MD[b]

In this prospective study of 30 children with ASD, fever greater than 100.4ºF 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

Examples: Metabolic problems

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

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

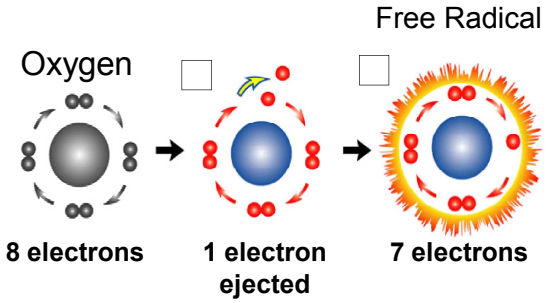
Zecavati and Spence, 2009 Curr Neurol Neurosci Rep 9(2):129-36

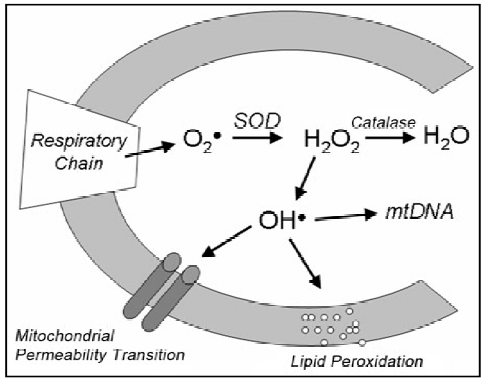
Metabolic abnormalities: ASD

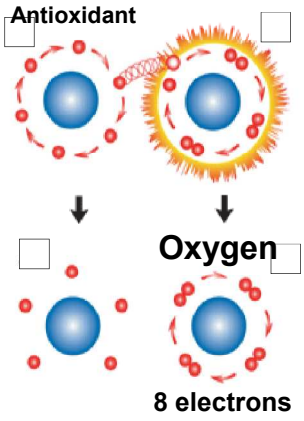
- Cerebral Folate Deficiency
- Mitochondrial Dysfunction
- Oxidative stress
- Impaired methylation / sulphation
- Inflammation
- Seizures
- Hypothyroidism: ASD and ADHD
- Deficiencies: iron (ASD and ADHD)

Oxidative Stress

Oxidative Stress







Brain Region-Specific Changes in Oxidative Stress and Neurotrophin Levels in Autism Spectrum Disorders (ASD)

Elizabeth M. Sajdel-Sulkowska · Ming Xu · Woody McGinnis · Noriyuki Koibuchi

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

Oxidative pathways as a drug target for the treatment of autism

Kristi-Ann Villagonzalo†, Seetal Dodd, Olivia Dean, Kylie Gray, Bruce Tonge & Michael Berk

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.

Villagonzalo et al., 2010 Expert Opin Ther Targets 14(12):1301-10

Article highlights.

- Current treatment options for autism are limited, and there is a need for proven, pathophysiologically-based treatments.
- Recent evidence indicates a potential role for oxidative stress in the pathophysiology of autism, based on:
  - abnormalities in transmethylation and transsulfuration
  - altered activity of oxidants and antioxidants
  - impaired heavy metal detoxification
  - mitochondrial dysfunction and impaired energy generation
  - genetic links between oxidative pathways and autism
- Antioxidant therapy may be effective in improving redox and behavioural outcomes in autism.

This box summarizes key points contained in the article.

Villagonzalo et al., 2010 Expert Opin Ther Targets 14(12):1301-10

Testing: Oxidative Stress

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

Suggested Antioxidant Doses

Table 1

Doses of antioxidants and other supplements (based on the studies reviewed):

Vitamin C: 100 mg/kg/day

Acetyl-L-carnitine: 50-100 mg/kg/day

L-carnosine: 200-400 mg twice a day

Pycnogenol: 1-2 mg/kg/day

Methylcobalamin injections: 75 mcg/kg 2-3 times per week

Folinic acid: 400 mcg twice a day

Omega-3 fatty acids: approx. 800 mg/day EPA and approx. 800 mg/day DHA

Zinc: 20-40 mg/day of elemental zinc

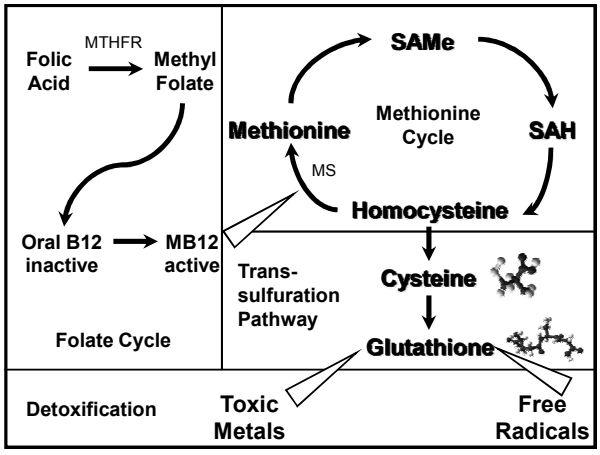
Melatonin: 1-3 mg, 30 minutes before bedtime

Magnesium: 6 mg/kg/day

Vitamin B-6: 0.6 mg/kg/day

Rossignol, 2009 Autism File 32:8-11

Impaired Methylation and Sulphation



Metabolic Endophenotype and Related Genotypes are Associated With Oxidative Stress in Children With Autism

Plasma methionine and the ratio of S-adenosyl-methionine (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

Abnormal Transmethylation/transsulfuration Metabolism and DNA Hypomethylation Among Parents of Children with 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.

James et al., 2008 J Autism Dev Disord 38(10):1966-75

Efficacy of methylcobalamin and folinic acid treatment on glutathione redox status in children with autism[1–3]

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.

James et al., 2009 Am J Clin Nutr 89(1):425-30

The effect of polyphenolic extract from pine bark, Pycnogenol®, on the level of glutathione in children suffering from attention deficit hyperactivity disorder (ADHD)

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.

Dvorakova et al., 2006 Redox Rep 11(4):163-72

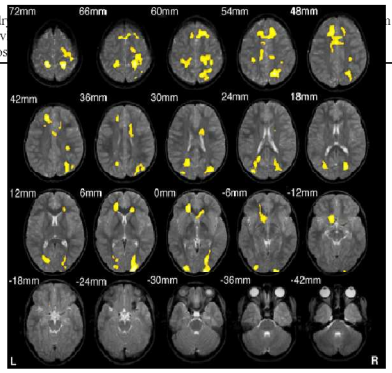
Increasing Glutathione

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

Inflammation

White matter abnormalities in autism detected through transverse relaxation time imaging☆

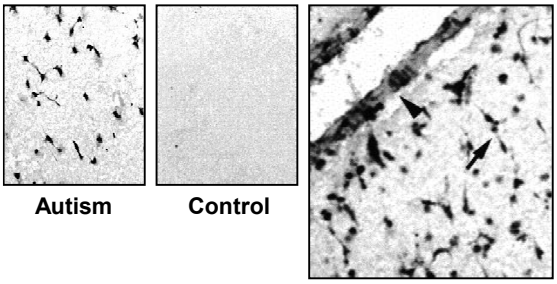
Janet Hendr… William Pav… Dick J. Dros… …n Rajakumar,[b]



Hendry et al., 2006 NeuroImage 29:1049-57

Serum autoantibodies to brain in Landau-Kleffner variant, autism, and other neurologic disorders

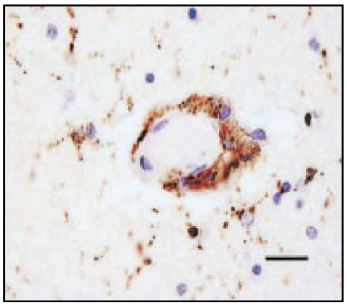
Anne M. Connolly, MD, Michael G. Chez, MD, Alan Pestronk, MD, Susan T. Arnold, MD, Shobhna Mehta, BSc, and Ruthmary K. Deuel, MD



Autism **Control**

Connolly et al., 1999 J Pediatr 134:607-13

Autism and Neuroinflammation



Perivascular macrophages and microglia

Vargas et al., 2005 Ann Neurol 57(1):67-81

Autism Severity and Temporal Lobe Functional Abnormalities

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.

Gendry Meresse et al., 2005 Ann Neurol 58:466-69

Brain Perfusion in Autism Varies with Age

James Wilcox[a] Ming T. Tsuang[b] Elizabeth Ledger[a] James Algeo[a] Thomas Schnurr[c]

[a]Department of Psychiatry, Texas Tech University Health Sciences Center, El Paso, Tex. [b]Harvard Medical School, Boston, Mass., USA

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

Selected areas of hypoperfusion in autism and clinical correlations

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

Original Articles

Elevation of Tumor Necrosis Factor-Alpha in Cerebrospinal Fluid of Autistic Children

Table 2. Tumor necrosis factor-alpha levels in serum and cerebrospinal fluid

Patient	Autoimmune Treatment	CSF (pg/mL)	Serum (pg/mL)	CSF/Serum Ratio
1	No	124	1.6	77.5
2	No	140	2.0	70.0
3	No	181	8.2	22.1
4	No	16	2.1	7.6
5	No	155	2.7	57.4
6	No	385	1.4	275
7	Yes	12	1.7	7.1
8	Yes	13	1.3	10.0
9	Yes	11	1.3	8.5
10	Yes	4	2.3	1.7
	Mean	104.1	2.5	53.7
	S.D.	121.3	2.3	

Chez et al., 2007 Pediatr Neurol 36(6):361-5

Inflammation: Testing

Urinary levels of neopterin and biopterin in autism

Table 1

Urinary neopterin and biopterin levels in autistic children, their siblings and control children

	Neopterin (μmol/mol creatinine)	Biopterin (μmol/mol creatinine)
Autistic children ($n = 14$)	3116 ± 686*	3691 ± 882**
Siblings ($n = 21$)	1490 ± 346	2923 ± 626**
Control children ($n = 16$)	908 ± 201	359 ± 80

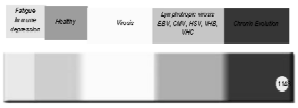
Data are the mean ± SEM. Significantly different from controls: *$P < 0.01$; **$P < 0.001$.

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

Urinary Neopterine Profile

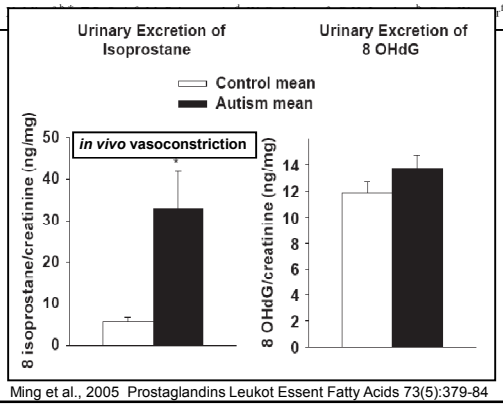
Immune system Methode : HPLC

	patient µmole / mole Cr	reference	result
urinary Neopterine (NEO)	1148	110 180	strongly increased cellular immunity activation
Urinary Biopterin (bM)	241		
Biopterin / Neopterin	0,2	>2	decreased ratio



**Neopterin is secreted by monocytes-macrophages stimulated by interferon-gamma and eradicates Th1 lymphocytes immune response. Its a reactive marker of cellular mediated immunity. It raises if level reflects cellular immunity weakening; increased level is positively correlated with infectious, inflammatory, immune and neoplastic disease evolutivity.

Increased excretion of a lipid peroxidation biomarker in autism



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

26/02/2008

Membrane Oxidative Damage

Urinary IsoprostaneF2-alpha

LC/MS-MS-immunoaffinity cartrige extraction -deuterated standard

8-iso-PGF2 alpa	**255** ng/gCr	80-160

Increased oxidative stress damage

urinary creatinin 630 mg/l

Other tests

- C-reactive protein / Sed rate
- Platelet count
- GI: fecal calprotectin / lactoferrin

- Inflammatory comorbidities:
  - Eczema
  - Asthma
  - Allergies

Treatment: Inflammation

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 stereotypies, 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.

Shenoy et al., 2000 J Pediatr 136(5):682-7

18. Pulse High-Dose Steroids as Combination Therapy with Valproic Acid in Epileptic Aphasia Patients with Pervasive Developmental Delay or Autism

A prospective study was done with 44 children with language regression and abnormal Digitrace 24 EEG epileptiform activity in sleep. All the patients were treated with a form of Depakote or Depakene for 8 to 12 weeks and were reassessed with a 24-hour EEG before the addition of weekly bolus high-dose prednisone or methylprednisolone (10 mg/kg/wk). Results of poststeroid add-on treatment were available for 25 cases. Of these patients, EEG showed further improvement in 60% (n = 15), with no improvement seen in 40% (n = 10). Clinical speech data showed the combination of Depakote/Depakene and pulse dose steroid treatment yielding improvement in 82% (n=36). Side effects were unremarkable with no cushingoid complications even after 18 months of therapy.

Chez et al., 1998 Annals Neurology 44(3):539

Case study **Open Access**

Effect of pioglitazone treatment on behavioral symptoms in autistic children

Marvin Boris*[1], Claudia C Kaiser[2], Allan Goldblatt[1], Michael W Elice[1], Stephen M Edelson[3], James B Adams[4] and Douglas L Feinstein[2]

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.

Boris et al., 2007 J Neuroinflammation 4:3

Spironolactone might be a desirable immunologic and hormonal intervention in autism spectrum disorders

Jan
Jan

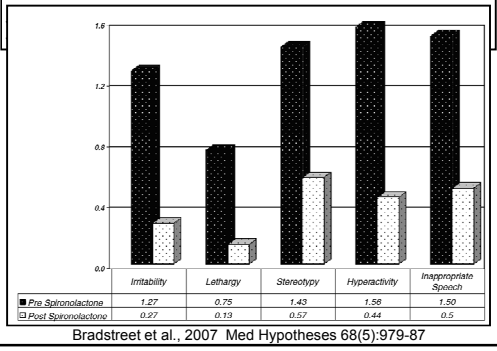
Table 2 Summary of the proposed effects of spironolactone on autism findings

Clinical finding	Autism finding	Effect of spironolactone
Interferon gamma	↑ [19]	↓ [55]
TNF-α	↑ [24,25]	↓ [54,55]
MCP-1	↑ [34]	↓ [54,56]
Inflammation	↑ [27,34]	↓ [53,55]
Oxidative stress	↑ [57]	↓ [62]
Testosterone effects	↑[a] [5–7]	↓ [59]

[a] Elevated in a subset of autistic individuals.

Bradstreet et al., 2007 Med Hypotheses 68(5):979-87

Spironolactone might be a desirable immunologic and hormonal intervention in autism spectrum disorders



Bradstreet et al., 2007 Med Hypotheses 68(5):979-87

Reduced Levels of Immunoglobulin in Children With Autism Correlates With Behavioral Symptoms

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 (0.670.06mg/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).

Heuer et al., 2008 Autism Res 1(5):275-283

Improvement in children with autism treated with intravenous gamma globulin

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.

Boris et al., 2006 J Nut Environ Med 15(4):1-8

Adaptive and Innate Immune Responses in Autism: Rationale for Therapeutic Use of Intravenous Immunoglobulin

Sudhir Gupta · Daljeet Samra · Sudhanshu Agrawal

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.

Gupta et al., 2010 J Clin Immunol

Opioid-immune interactions in autism: behavioural and immunological assessment during a double-blind treatment with naltrexone

Renato SCIFO *(a)*, Matteo CIONI *(b)*, Alfredo NICOLOSI *(c)*, Nunzio BATTICANE *(b)*, Cataldo TIROLO *(b)*, Nuccio TESTA *(b)*, Maria C. QUATTROPANI *(d)*, Maria C. MORALE *(b)* Francesco GALLO *(e)* and Bianca MARCHETTI *(e)*

- **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**

Scifo et al., 1996 Ann Ist Super Sanita 32(3):351-9

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

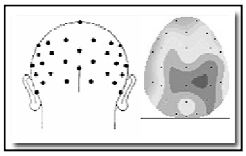
Seizures: Definition

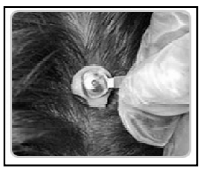
- **Episodes of disturbed brain function that cause changes in attention or behavior**
- **Caused by abnormally excited electrical signals that disrupt the smooth-running pattern of electrical activity in the brain causing overload**
- **Epilepsy: recurrent seizures**

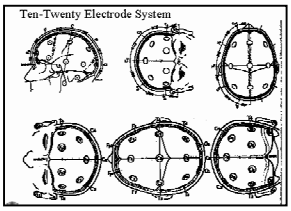
Seizures: Symptoms

- **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)**

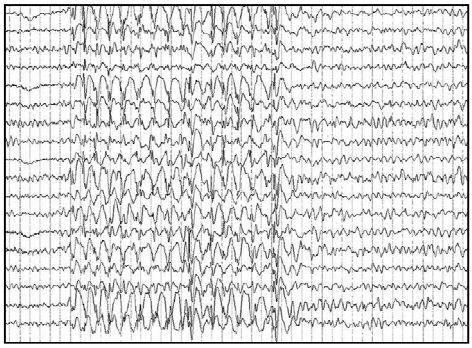
Scalp EEG Data Acquisition







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

SLEEP DISORDERS, EPILEPSY, AND AUTISM

Beth A. Malow*

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.

Malow, 2004 Ment Retard Dev Disabil Res Rev 10(2):122-5

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

Jeffrey D. Lewine, Richard Andrews, Michael Chez, Arun-Angelo Patil, Orrin Devinsky, Michael Smith, Andres Kanner, John T. Davis, Michael Funke, Greg Jones, Brian Chong, Sherri Provencal, Michael Weisend, Roland R. Lee, William W. Orrison and Jr, MD

Pediatrics 1999;104;405-418
DOI: 10.1542/peds.104.3.405

- When MEG found epileptiform abnormalities
  - 50% had a normal 1 hour EEG
  - 19% had a normal 24 hour EEG
  - When epileptiform activity was present in the ASDs, the same intra/perisylvian regions seen to be epileptiform in LKS were active in 85% of the cases
  - Most ASD cases had multifocal areas

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

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

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

ANNALS OF CLINICAL PSYCHIATRY 2009;21(3):XX-XX REVIEW ARTICLE

www.aacp.com/pdf%2F2104%2F2104ACP_Review2.pdf

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 B_6/magnesium, elimination diets, chelation, cyproheptadine, famotidine, glutamate antagonists, acupuncture, auditory integration training, massage, and neurofeedback.

Rossignol, 2009 Annals Clin Psych 21(4):213-236

TABLE 1

The top 20 complementary and alternative medicine treatments for children with an ASD, excluding diets

Ranking	Treatment	Better[a] (%)	No change[b] (%)	Worse[c] (%)	No. responses[d]	Grade
1	Chelation	74	23	3	803	C
2	MB12 injections	67	26	7	170	D
3	Melatonin	65	27	8	1105	A
4	B_{12} (oral)	61	32	7	98	D
5	HBOT	60	34	5	134	B
6	Digestive enzymes	58	39	3	1502	D
7	Fatty acids	56	41	2	1169	C
8	MB12 (nasal)	56	29	15	48	D
9	Cod liver oil	51	45	4	1681	C
10	Vitamin B_6 (PLP)	51	37	12	529	C
11	Zinc	51	47	2	1989	N
12	B_6/magnesium	48	48	4	6634	C
13	Folic acid	43	53	4	1955	D
14	Vitamin B_6	43	52	4	927	N
15	Vitamin C	43	55	2	2397	B
16	DMG	42	51	8	5807	D
17	TMG	42	43	15	803	D
18	Transfer factor	42	48	10	174	D
19	Vitamin A	41	57	2	1127	D
20	5-HTP	40	47	13	343	D

Rossignol, 2009 Annals Clin Psych 21(4):213-36

TABLE 7

Summary of treatments and their effects on certain autistic behaviors

Speech/communication	Carnitine Carnosine GFCF diet Alpha-2 adrenergic agonists Cyproheptadine Glutamate antagonists AIT	Tetrahydrobiopterin B6/magnesium AI HBOT Famotidine Music therapy Neurofeedback
Autistic behavior	Carnosine B_6/magnesium Probiotics GFCF diet Alpha-2 adrenergic agonists Cyproheptadine Vision therapy	Piracetam Folic acid/B_{12} Digestive enzymes AI HBOT Music therapy
Social interaction	Tetrahydrobiopterin B6/magnesium AI HBOT Famotidine Massage	Carnosine GFCF diet Naltrexone Oxytocin Glutamate antagonists Neurofeedback

Rossignol, 2009 Annals Clin Psych 21(4):213-36

Stereotypy	Vitamin C B6/magnesium Alpha-2 adrenergic agonists Famotidine AIT	Omega 3 fatty acids Naltrexone Cyproheptadine Glutamate antagonists Massage
Hyperactivity	Omega 3 fatty acids AI Alpha-2 adrenergic agonists Glutamate antagonists Massage	Magnesium Naltrexone Chelation AIT
Eye contact	Tetrahydrobiopterin AI Famotidine	Omega 3 fatty acids HBOT Music therapy
Attention	Omega 3 fatty acids Alpha-2 adrenergic agonists Music therapy	AI Glutamate antagonists
Sleep	Melatonin Multivitamin Alpha-2 adrenergic agonists	Carnitine Iron

AI: Acetylcholinesterase inhibitors; AIT: auditory integration training; GFCF: gluten-free, casein-free diet; HBOT: hyperbaric oxygen treatment;

Rossignol, 2009 Annals Clin Psych 21(4):213-36

BIOMEDICAL

DIAGNOSIS AUTISM: **NOW WHAT?** A SIMPLIFIED BIOMEDICAL APPROACH

By Dan Rossignol, MD, FAAFP

Rossignol, 2009 Autism File 32:8-11