Biomedical Problems in Autism and Dietary Considerations

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Nourishing Hope
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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.

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: has + and - symptoms
- Therefore, the diagnosis of autism tells us nothing about the potential causes of the disorder

Autism
- symptoms (too little)
  - Speech delay
  - Impaired social interaction
  - Poor eye contact
  - Impaired attention
  - Generally correspond to lower brain activity and cerebral hypoperfusion

+ symptoms (too much)
  - Hyperactivity
  - Self-stimulatory activity
  - Obsessive-compulsive behavior
  - Aggression
  - Generally correspond to increased brain perfusion and activity

Proteins
Amino Acids
Polysaccharides
Monosaccharides
Fats
Fatty Acids

Carnitine
Citric acid cycle
NAD+
NADH
AcetylCoA
ADP
ATP
Oxidative Phosphorylation

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Approved Medications: ASD

- Risperidone (Risperdal®)
- Aripiprazole (Abilify®)
- Both are atypical antipsychotic medications approved for treating irritability associated with ASD and thus do not treat core autistic symptoms or behaviors
- There are currently no approved medications for the core symptoms of ASD

Problems in Autism

- Mitochondrial dysfunction
  – Production of energy (ATP) from food and oxygen
- Gastrointestinal problems
  – Inflammation
  – Constipation
  – Diarrhea
  – Dysbiosis
- Dietary issues
- Food allergies
- Cholesterol deficiency
- Nutritional deficiencies

Gut-Brain Connection

Science NOW: UP TO THE MINUTE NEWS FROM SCIENCE

Getting Fat? Blame Your Gut Bugs

by Chloeth Pinnal on 4 November 2006, 12:00 AM | Permanent Link | 5 Comments

INSANITY PROCEEDING FROM THE COLON.

Read before the Chicago Medical Society, July 25, 1889.
BY HAROLD N. MOYER, M.D.,
LECTURER ON PHYSIOLOGY, RUSH MEDICAL COLLEGE, CHICAGO.

Moyer, 1889 JAMA 13(7): 230
An obscure relationship between disorders of the digestive tract and joint affections has long been recognized by clinicians, and in the last decade some of these relations have become better understood. It is now known that severe cases of arthritis may occasionally be completely relieved by preventing absorption of intestinal contents in the large intestine. This may be accomplished by intestinal lavage, purging, regulation of diet, and by operations on the colon that cause fecal material to be discharged through artificial openings, thus putting the lower portion of the intestine entirely out of function.

The purpose of this article is to present a report of the result of the treatment of mental disease by the use of colonic irrigation at the Gardner State Colony and to call attention to the possible wider value of this procedure in medical and surgical problems.

**Human GI tract**

- Humans have 10^{13} human cells and 10^{14} bacteria
- There is a symbiotic association between humans and their intestinal microbial flora
  - Crucial for nutrient assimilation
  - Important for development of the innate immune system

"The ‘we’ refers to the wild profusion of bacteria, fungi and viruses that colonize the human body. These unseen passengers number in the trillions. According to one common estimate, the human gut contains at least a kilogram of bacteria alone. They contribute so much to human biology that it is difficult to say where the body ends and the microbes begin — which is why several massive projects have now started up to characterize the human microbiota in its entirety"
Gastrointestinal Problems in Autism

Horvath et al., 1999  J Pediatr 135(5): 559-63

The most frequent gastrointestinal complaints were chronic diarrhea, gaseousness, and abdominal discomfort and distension. Histologic examination in these 36 children revealed grade I or II reflux esophagitis in 25 (69.4%), chronic gastritis in 15, and chronic duodenitis in 24. Low intestinal carbohydrate digestive enzyme activity was reported in 21 children (58.3%), although there was no abnormality found in pancreatic function. CONCLUSIONS: Unrecognized gastrointestinal disorders, especially reflux esophagitis and disaccharide malabsorption, may contribute to the behavioral problems of the non-verbal autistic patients.

Adams et al., 2011 BMC Gastroenterol 11(1):22

Aims: To evaluate autistic children with GI complaints and aggression or self-injurious behavior in order to determine if these behaviors may be symptoms of GER. Methods: Six consecutive autistic children (ages 8–19 years) undergoing endoscopy and scheduled for BRAVO (wireless) pH probe were evaluated for histology and pH meter results. Findings: GER was identified in 5 of 5 patients tested by BRAVO pH testing. Esophagitis was seen in 3 of 6 patients biopsied. Conclusions: Aggressive or self-injurious behavior may be a manifestation of pain from GER and should prompt consideration of further investigation.


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.
Constipation

Afzal et al., 2003  Pediatrics 112(4):939-42

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.

Atzal et al., 2003  Pediatrics 112(4):939-42

Atzal et al., 2003 Pediatrics 112(4):939-42

Krigsman, 2007  Medical Veritas 4:1528-36
Treatment of Constipation
- Magnesium citrate
- Vitamin C
- Aloe vera juice
- Carnitine
- Lactulose
- Miralax
- Enemas

Diarrhea

Diarrhea: Causes
- Infections
- Food
- Medications
- Nutritional supplements
- Functional diarrhea
- Dysbiosis

Dysbiosis

Growing evidence suggests that the microbiome conditions host immunity to microbes and xenobiotics, and regulates autoimmune responses that can affect the central nervous system (CNS). An increased prevalence of familial autoimmunity, exposure to pathogens prenatally and postnatally, and findings of antibrain antibodies is common in disorders as diverse as schizophrenia, obsessive-compulsive disorder and autism, and suggests that differences in exposure timing and genetic vulnerability toward autoimmunity are important determinants of neuropsychiatric outcomes.

SUMMARY: Microbes, both pathogenic and commensal, can induce autoantibodies that bind to brain and affect behavior in susceptible hosts.

Hornig, 2013  Curr Opin Rheumatol

Some cases of late-onset (regressive) autism may involve abnormal flora because oral vancomycin, which is poorly absorbed, may lead to significant improvement in these children. Fecal flora of children with regressive autism was compared with that of control children, and clostridial counts were higher. The number of clostridial species found in the stools of children with autism was greater than in the stools of control children. Children with autism had 9 species of Clostridium not found in controls, whereas controls yielded only 3 species not found in children with autism. In gastric and duodenal specimens, the most striking finding was total absence of non-spore-forming anaerobes and microaerophilic bacteria from control children and significant numbers of such bacteria from children with autism.

Finegold et al., 2002  Clin Infect Dis 35(Suppl 1):S6-S16
A compound identified as HPHPA was found in higher concentrations in urine samples of children with autism compared to age and sex appropriate controls and in an adult with recurrent diarrhea due to Clostridium difficile infections. The highest value measured in urine samples was 7500 mmol/mol creatinine, a value 300 times the median normal adult value, in a patient with acute schizophrenia during an acute psychotic episode. The psychosis remitted after treatment with oral vancomycin with a concomitant marked decrease in HPHPA. The significance of this compound is that it is a probable metabolite of m-tyrosine (3-hydroxyphenylalanine), a tyrosine analog which depletes brain catecholamines and causes symptoms of autism...

Shaw, 2010  Nutr Neurosci 13(3): 135-43

6 yo girl with autism

- Speech: knows 30 words, occasionally puts 2 together
- Stimming: moderate-severe
- OCD: moderate-severe
- Social interaction: poor
- Sleep: night-time awakening
- GI: loose stools, smell bad, increased gas, undigested food

Microbial Panel

<table>
<thead>
<tr>
<th>Compound</th>
<th>Reference Range mmol/mol creatinine</th>
<th>Patient Value mmol/mol creatinine</th>
<th>Yeast/Flame</th>
<th>Bacterial</th>
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<tr>
<td>ceramide</td>
<td>0.0 - 1.0</td>
<td>1.42</td>
<td>H</td>
<td></td>
</tr>
<tr>
<td>5-hydroxytryptophan</td>
<td>0.0 - 10.0</td>
<td>8.99</td>
<td>H</td>
<td></td>
</tr>
<tr>
<td>3-creatinic</td>
<td>0.0 - 100.0</td>
<td>5.83</td>
<td>H</td>
<td></td>
</tr>
<tr>
<td>formic acid</td>
<td>0.0 - 5.0</td>
<td>3.91</td>
<td>H</td>
<td></td>
</tr>
<tr>
<td>fumaric</td>
<td>0.0 - 100.0</td>
<td>1.19</td>
<td>H</td>
<td></td>
</tr>
<tr>
<td>malonic acid</td>
<td>0.0 - 100.0</td>
<td>11.61</td>
<td>H</td>
<td></td>
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<tr>
<td>carboxylic acid</td>
<td>0.0 - 100.0</td>
<td>137.06</td>
<td>H</td>
<td></td>
</tr>
<tr>
<td>2-hydroxyphosphonic acid</td>
<td>0.0 - 10.0</td>
<td>0.79</td>
<td>H</td>
<td></td>
</tr>
<tr>
<td>HPHPA</td>
<td>0.0 - 150.0</td>
<td>525.83</td>
<td>H</td>
<td></td>
</tr>
<tr>
<td>NMA analog</td>
<td>0.0 - 10.0</td>
<td>10.75</td>
<td>H</td>
<td></td>
</tr>
</tbody>
</table>

6 yo girl with autism

Treatments to consider:

- Yeast: antifungal
- Clostridia
  - Flagyl 125-250 mg tid
  - Vancomycin 125-250 mg tid
  - Alinia 100-200 mg bid
- Probiotics
- Digestive enzymes
- Anti-inflammatories
Yeast: Treatments

- Antifungals
  - Fluconazole (Diflucan)
  - Ketoconazole (Nizoral)
  - Nystatin *
  - Amphotericin B *
  - Itraconazole (Sporanox)
  - Terbinafine (Lamisil)
* not absorbed

6 yo girl with autism

- Treatment with nystatin and flagyl (3 weeks) led to improvements in stimming/OCD and some decrease in abdominal distension and loose stools
- Placed on 2 week prednisone taper (starting at 2 mg/kg/day): Almost complete clearing of GI problems, moderate improvement in speech
- Placed on Spironolactone 2 mg/kg/day

Dietary Problems


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.

Hadjivassiliou et al., 2002 J Neurol Neurosurg Psychiatry 72(5):560-3

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
Five out of one hundred and fifty subjects (3.3%) were diagnosed with CD on the basis of positive serologic tests and histopathological findings. This is significantly higher \((p = .014)\) in comparison to CD prevalence for the general paediatric population of 1:106 (Binomial Test). In conclusion, our data suggest that, within the context of research, the screening for CD is recommended in all children with autism, even if no gastrointestinal symptoms are present.

Barcia et al., 2008 J Autism Dev Disord 38(2):407-8

Atladottir et al., 2009 Pediatrics 124(2):687-94

The study cohort consisted of all of the children born in Denmark from 1993 through 2004 (689 196 children). RESULTS: A total of 3325 children were diagnosed with ASDs, of which 1089 had an infantile autism diagnosis. Increased risk of ASDs was observed for children with a maternal history of rheumatoid arthritis and celiac disease. Also, increased risk of infantile autism was observed for children with a family history of type 1 diabetes. A significant association between maternal history of celiac disease and ASDs was observed for the first time.

Zelnik et al., 2004 Pediatrics 113(6):1672-6

Patients with CD were more prone to develop neurologic disorders (51.4%) in comparison with control subjects (19.9%). These disorders include hypotonia, developmental delay, learning disorders and ADHD, headache, and cerebellar ataxia. Epileptic disorders were only marginally more common in CD. In contrast, no difference was found in the prevalence of tic disorders in both groups. Therapeutic benefit, with gluten-free diet, was demonstrated only in patients with transient infantile hypotonia and migraine headache.

Zelnik et al., 2004 Pediatrics 113(6):1672-6

The present study demonstrates a previously unrecognised link between gluten sensitivity and TLE with HS. This association was very robust in this well-characterised group of patients; thus gluten sensitivity should be added to the list of potential mechanisms leading to intractable epilepsy and HS.

Paltola et al., 2009 J Neurol Neurosurg Psychiatry 80(6):626-30

The ScanBrit randomised, controlled, single-blind study of a gluten- and casein-free dietary intervention for children with autism spectrum disorders

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 Nutr Neurosci 13(2), in press
METHODS: This study analyzes parental report data collected using a 90-item online questionnaire from 387 parents or primary caregivers of children diagnosed with ASD on the efficacy of the GFCF diet. RESULTS: Overall, diet efficacy among children whose parents reported the presence of GI symptoms, food allergy diagnoses, and suspected food sensitivities included greater improvement in ASD behaviors, physiological symptoms, and social behaviors compared with children whose parents reported none of these symptoms, diagnoses, or sensitivities (P < 0.05). Parental report of strict diet implementation, indicated by complete gluten/casein elimination and infrequent diet errors during and outside of parental care, also corresponded to improvement in ASD behaviors, physiological symptoms, and social behaviors (P < 0.05).

We report the history of a child with autism and epilepsy who, after limited response to other interventions following her regression into autism, was placed on a gluten-free, casein-free diet, after which she showed marked improvement in autistic and medical symptoms. Subsequently, following pubertal onset of seizures and after failing to achieve full seizure control pharmaceutically, she was advanced to a ketogenic diet that was customized to continue the gluten-free, casein-free regimen. On this diet, while still continuing on anticonvulsants, she showed significant improvement in seizure activity. This gluten-free casein-free ketogenic diet used medium-chain triglycerides rather than butter and cream as its primary source of fat.

Jyonouchi et al., 2005  Neuropsychobiology 51(2):77-85

Sun et al., 1999  Autism 3(1):67-83

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Bone development, casein-free diet use, supplements, and medications were assessed for 75 boys with autism or autism spectrum disorder, ages 4-8 years. The 12% of the boys on casein-free diets had an overall % deviation of -18.9 +/- 3.7%, nearly twice that of boys on minimally restricted or unrestricted diets (-10.5 +/- 1.3%, p < .04), although even for boys on minimally restricted or unrestricted diets the % deviation was highly significant (p < .001).

Euguelou et al., 2003 J Child Neurol 18(2):113-8

A pilot prospective follow-up study of the role of the ketogenic diet was carried out on 30 children with autistic behavior. The diet was applied for 6 months, with continuous administration for 4 weeks, interrupted by 2-week diet-free intervals. Seven patients could not tolerate the diet, whereas five other patients adhered to the diet for 1 to 2 months and then discontinued it. Of the remaining group who adhered to the diet, 18 of 30 children (60%), improvement was recorded in several parameters and in accordance with the Childhood Autism Rating Scale.

Food Allergies

- IgE: immediate
  - Often result in skin problems, hives, swelling, breathing problems, etc. This can be tested using a skin test or blood test
- IgG or IgA: delayed or intolerance
  - Can result in more varied or vague symptoms like discomfort, stomach problems, sleep problems, joint pain, ear infections, or hyperactivity and behavioral problems

Food Sensitivities

Diagnosing food sensitivities

- IgE allergy testing (RAST tests, skin prick tests)
- IgG testing (ELISA food sensitivity panels)
- Elimination diet trials
  - In my experience, this is the most reliable method.
We undertook a randomised, double-blinded, placebo-controlled, crossover trial to test whether intake of artificial food colour and additives (AFCA) affected childhood behaviour. Artificial colours or a sodium benzoate preservative (or both) in the diet result in increased hyperactivity in 3-year-old and 8/9-year-old children in the general population.

McCann et al., 2007 Lancet 370(9598):1560-7

The aim of the present study has been to verify the efficacy of a cow’s milk free diet (or other foods which gave a positive result after a skin test) in 36 autistic patients. We noticed a marked improvement in the behavioural symptoms of patients after a period of 8 weeks on an elimination diet. Our results lead us to hypothesize a relationship between food allergy and infantile autism as has already been suggested for other disturbances of the central nervous system.

Lucarelli, 1995 Panminerva Med 37(3):137-41

**Food allergy and infantile autism**

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Lucarelli, 1995 Panminerva Med 37(3):137-41

**Treating food sensitivities**

- **Diet modification**
- **Food elimination and reintroduction**
- **Rotation of foods**
- **Digestive enzymes**
- **Probiotics**
- **Supplements**
  - Quercitin
  - Isoquercitin
  - Pycnogenol

**Treating food sensitivities**

- **Immune modulators**
  - Antihistamines (H1 and H2 blockers), Ketotifen
  - Leukotriene inhibitors (Singulair)
  - Mast cell stabilizers (Cromolyn, Gastrocrom)

**Cholesterol**
Low Cholesterol

Zhang et al., 2005 Am J Epidemiol 161(7):691-9

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).

Zhang et al., 2005 Am J Epidemiol 161(7):691-9

Autism: The role of cholesterol in treatment

ALINKA ANEJA & ELAINE TIERNEY

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.

Anjia and Tierney, 2008 Int Rev Psychiatry 20(2):165-70

DIAGNOSIS AUTISM: NOW WHAT? A SIMPLIFIED BIOMEDICAL APPROACH

By Dan Rossignol, M.D. TALLIP

Novel and emerging treatments for autism spectrum disorders: A systematic review


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, tetralysinol, probiotics, 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, multivitamins/minerals complex, piracetam, polyunsaturated fatty acids, vitamin E, magnesium, elimination diets, chelation, cyproheptadine, simvastatin, glutathione, arginine, acupuncture, auditory integration training, massage, and neurofeedback.


TABLE 7: Summary of treatments and their effects on certain autistic behaviors

Speech/communication

Camitine

GCFS diet

Alpha-2 adrenergic agonists

Cannabinoids

Glutamate antagonists

AHT

Tetrahydrobiopterin

Eliptol

Mithoxy-therapy

Respirol

Autistic behavior

Carnitine

Glutamate

Prednisone

GFCS diet

Alpha-2 adrenergic agonists

Cyproheptadine

Vision therapy

Social interaction

Tetrahydrobiopterin

GCFS diet

AHT

Mithoxy-therapy

Respirol


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<tr>
<th>Domain</th>
<th>Vitamin</th>
<th>Niacinamide</th>
<th>Alpha L-Adrenergic agonists</th>
<th>Flavonoids</th>
<th>Omega 3 fatty acids</th>
<th>Magnesium</th>
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<th>Glutamate antagonists</th>
<th>Music therapy</th>
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