

The Medical Side of the GF/CF Diet

What is being treated and why it isn't just "Autism"

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Disclaimer

- Information is for educational purposes only.
- Information contained in presentation is not to be taken as medical advice.
- All medical decisions need to be discussed with your personal healthcare provider.

What is "Autism"

DSM IV Criteria for Autism⁽¹⁾

- (B) A total of six (or more) items from (A), (B), and (C), with at least two from (A), and one each from (B) and (C)
 - (A) qualitative impairment in social interaction, as manifested by at least two of the following:
 - Marked impairments in the use of multiple nonverbal **behaviors** such as eye-to-eye gaze, facial expression, body posture, and gestures to regulate social interaction
 - Failure to **develop peer relationships** appropriate to developmental level
 - Lack of spontaneous seeking to **share enjoyment, interests, or achievements** with other people, (e.g., by a lack of showing, bringing, or pointing out objects of interest to other people)
 - Lack of **social or emotional reciprocity** (note: in the description, it gives the following as examples: not actively participating in simple social play or games; preferring solitary activities; or involving others in activities only as tools or "mechanical" aids)

DSM IV Criteria for Autism

- (B) qualitative impairments in communication as manifested by at least one of the following:
 - Delay in, or total lack of, the **development of spoken language** (not accompanied by an attempt to compensate through alternative modes of communication such as gesture or mime)
 - In individuals with adequate speech, marked impairment in the ability to **initiate or sustain a conversation** with others
 - Stereotyped and repetitive** use of language or idiosyncratic language
 - Lack of varied, spontaneous make-believe **play or social imitative play** appropriate to developmental level

DSM IV Criteria for Autism

- (C) restricted, repetitive and stereotyped patterns of behavior, interests and activities, as manifested by at least two of the following:
 - encompassing preoccupation with one or more **stereotyped and restricted patterns** of interest that is abnormal either in intensity or focus
 - apparently **inflexible** adherence to specific, nonfunctional routines or rituals
 - stereotyped and repetitive **motor mannerisms** (e.g. hand or finger flapping or twisting, or complex whole-body movements)
 - persistent preoccupation with **parts of objects**
- (D) **Delays or abnormal functioning in at least one of the following areas, with onset prior to age 3 years:**
 - (A) social interaction
 - (B) language as used in social communication
 - (C) symbolic or imaginative play
- (E) **The disturbance is not better accounted for by Rett's Disorder or Childhood Disintegrative Disorder**

DSM IV Criteria for Autism

- What is **not** included in the criteria:
 - Gastrointestinal Symptoms
 - Food intolerances, picky eating, aversions
 - Food allergies
 - Constipation
 - Diarrhea
 - Posturing
 - Walking on toes, leaning over arms of chairs, couches, etc.
- The VAST majority of children with Autism, however, have the above symptoms.
 - Horvath K, et al. Gastrointestinal abnormalities in children with autistic disorder. *J Pediatr*. 1999 Nov; 135(5):559-63.
 - Horvath K, Perman JA. Autism and gastrointestinal symptoms. *Curr Gastroenterol Rep*. 2002 Jun; 4(3):251-6.

Question:

- Why then, when studies evaluate the effectiveness of the GF/CF diet, is the DSM-IV criteria used as a measure?

PEDIATRICS

OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

Evaluation, Diagnosis, and Treatment of Gastrointestinal Disorders in Individuals With ASD: A Consensus Report
Timothy Buie, Daniel B. Campbell, George J. Fuchs, III, Glenn T. Furuta, Joseph Levy, Judy Vandewater, Agnes H. Whitaker, Dan Atkins, Margaret L. Bauman, Arthur L. Beaulieu, Edward G. Carr, Michael D. Gershon, Susan L. Hyman, Piroop Jirapinyo, Harumi Jyonouchi, Kooreth Koorek, Rafail Kurlak, Pat Levitt, Susan E. Levy, Jeffrey D. Lewis, Katherine P. Maney, Marvin R. Nussinov, Aderbal Sabra, Barry K. Wershil, Sharon C. Weston, Lonnie Zeltzer and Hartard Winter
Pediatrics 2010;125(S1):S18
DOI: 10.1542/peds.2009-1878C

- Dr. Timothy Buie - Mass General Hospital
 - Lead a panel of experts that reviewed the current literature on GI disease and autism to come up with guidelines for treatment.

Consensus Report GI and Autism

- Agreement was made that there was **not enough evidence** to formulate guidelines.
 - The focus was turned to creating consensus statements to **direct and focus** future research and treatment.
 - 23 consensus statements, which were summarized into key take away messages in the paper.

Statement 1 (Key Statement)
 Individuals with ASDs who present with gastrointestinal symptoms warrant a thorough evaluation as would be undertaken for individuals without ASDs who have the same symptoms or signs. Evidence-based algorithms for the assessment of abdominal pain, constipation, chronic diarrhea, and gastroesophageal reflux disease (GERD) should be developed.

Consensus Report GI and Autism Take Away Messages

- Individuals with ASDs whose families report GI symptoms warrant a thorough GI evaluation.
- All of the common GI conditions encountered by individuals with typical neurologic development are also present in individuals with ASDs.
- The communication impairments characteristic of ASDs may lead to unusual presentations of GI disorders, including **sleep disturbances and problem behaviors**.
- Caregivers and healthcare professionals should be alert to the presentation of **atypical signs** of common GI disorders in patients with ASDs.
- If a person with an ASD is on a **restricted diet**, professional supervision can help to identify and treat nutritional inadequacy.
- Integrating **behavioral and nutritional approaches** can be advantageous in conceptualizing the role of pain as a setting event for problem behavior, facilitating diagnosis, and addressing residual pain symptoms to enhance quality of life.
- Genetic assays should be included as part of the data to be collected in research protocols. At present, there are inadequate data to establish a causal role for intestinal permeability, immunologic abnormalities, or food allergies in ASDs.

Media's Take Away Message

Report: Special Diets Do Not Help Autism- CBS News
 Study Says Digestive Problems Not More Common in Autistic Children, Refutes Link Between Digestion, Vaccine

Journal Says No Proof Special Diets Help ASDs who respond to dietary intervention

Autistic Children- ABC News



Panel finds no evidence that restricted diets help autistic children, but some parents disagree- NY Daily News

Panel finds no evidence that restricted diets help autistic children, but some parents disagree- NY Daily News

support the use of a casein-free diet, a gluten-free diet, or combined gluten-free, casein-free (GF/CF) diet as primary treatment for individuals with ASDs.

My Take Away Message

- To say that we prescribe the GF/CF diet for **"Autism"** is an oversimplification of our evaluation, decision making, and treatment processes.
 - Comparable to a mechanic fixing one car part over and over again rather than opening up the car's hood, running needed diagnostic tests, and fixing the specific problems identified.

Why use a GF/CF diet in Autism?

- Balancing clinical judgement and research
 - Evidence-based medicine
 - Anecdotal evidence
 - Overwhelmingly positive
 - 2009 ARI (Autism Research Institute) survey
 - 69% of patients on GF/CF diet reported significant improvement
 - Only 3% got worse
 - Research
 - Many theories discussed, but the majority of the results were mixed and/or the strength of the study was small.
 - Consensus statement #12. More studies needed with better design to create more reproducible results.

GI symptoms and Autism

- Increased incidence of GI symptoms in Autistic children
 - Valentini McDermott M. et al. Frequency of gastrointestinal symptoms in children with autistic spectrum disorders and association with family history of autoimmune disease. *J Dev Behav Pediatr.* 2006 Apr 27 (2 Suppl):5128-36.
 - Horvath K. et al. Gastrointestinal abnormalities in children with autistic disorder. *J Pediatr.* 1999 Nov; 135(5):559-63.
 - Horvath K, Perrman JA. Autism and gastrointestinal symptoms. *Curr Gastroenterol Rep.* 2002 Jun 4(3):251-6.
 - Horvath K, Perrman JA. Autistic disorder and gastrointestinal disease. *Curr Opin Pediatr.* 2002 Oct 14(5):583-7.

Why use a GF/CF diet in Autism?

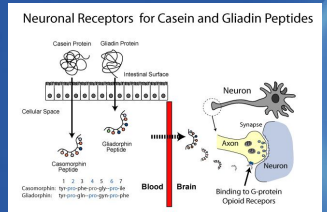
- Theories:
 - Opioid excess theory and DPP-IV deficiency
 - Chronic Inflammation from:
 - Allergies (IgE, IgG)
 - Toxicity
 - Chronic Infections
 - Present Research and Practice
 - Zonulin molecule and increased intestinal permeability
 - Cerebral Folate Receptor Autoantibodies

Opioid Excess Theory

- Origins from the 1960's research by Curtis Duhan
 - Speculated that the low incidence of schizophrenia in certain South Pacific Island societies was a result of diet low in wheat and milk based foods.
- Dr. Jack Panskeep (1979)
 - Showed similar association between this type of diet and autism
- Dr. Kalle Reichelt (1991, 2003, 2009)
 - Autistic children had elevated levels of peptides in their urine (including gliadomorphin and casomorphin) not found in urine of non-autistic children
 - Both are incomplete broken down peptides from gluten and casein proteins. They are very similar in structure to opioid molecules.
 - These findings led to the **Opioid excess theory**

Casomorphins/Gliadomorphins

Neuronal Receptors for Casein and Gliadin Peptides



The diagram illustrates the process where casein and gliadin proteins are broken down into peptides in the cellular space. Some of these peptides, specifically casomorphin and gliadomorphin, cross the intestinal surface and the blood-brain barrier. Once in the brain, they bind to neuronal receptors, which triggers a signal through the axon to the neuron.

Opioid Excess Theory DPP-IV Enzyme

- Alan Friedman Ph.D (2000)
 - Chemist for Johnson & Johnson
 - Pioneered studies into the potential role of Dipeptidyl Peptidase (DPP-IV) enzyme deficiency in autism.
 - Enzyme responsible for breaking down casomorphins and gliadomorphins is seemingly absent in patients with autism.
 - Theorized that there was a genetic deletion or environmental factor that was responsible for the lack of DPP-IV.
 - The gene responsible for this enzyme is distal to other suspected genes and is expressed in the kidney, small intestine, liver, and on the surface of WBC (CD26)

Opioid Excess Theory

- Alan Friedman Ph.D (2000)
 - Also found two other mu-opioids in the urine of autistic children
 - Dermorphin & Deltamorphin II
 - Found on the skin of poison-dart frogs in South America
 - Poison theorized to be from bacteria on the skin of the frogs, not the skin itself.
 - Same bacteria theorized to be present in the guts of autistic children

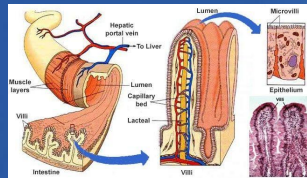
Chronic Inflammation

- Chronic inflammation of the small intestine in autistic patients is well documented and confirmed in the consensus report.
- The causes are debatable, but research suggests that underlying conditions may contribute, such as:
 - Food allergies (IgE, IgG)
 - Toxicity (Heavy metal, Pesticides, MSG)
 - Chronic Infections (Bacterial/fungal overgrowth, viral, parasitic)

Food Allergens

- Immune-mediated reactions
 - Food allergy- IgE mediated
 - Can trigger signs and symptoms such as digestive problems, hives or swollen airways. In some people, a food allergy can cause severe symptoms or even a life-threatening reaction known as anaphylaxis.
 - Food Sensitivities- IgG mediated
 - Associated with increased intestinal permeability allowing larger peptides to pass through the intestinal epithelium. The blood IgG antibodies do not recognize the larger peptides as nutrients and attack them as invaders.

Food Allergens



Food Allergens

- IgE vs. IgG
 - Symptoms of IgE vs. IgG mediated food allergy/sensitivity reactions

	IgE reaction	IgG reaction
Time Frame	Usually Immediate	Can take up to three days
Respiratory	Wheezing, difficulty breathing, coughing, tightness of the throat	Rhinitis, Sinusitis, Asthma
Skin	Hives, redness, itching, swelling of the lips and/or eyelids	Urticaria, eczema, atopic dermatitis, rashes
Neurologic	Headache, Mood disorders	Headache, Mood disorders, hyperactivity
Gastrointestinal	Stomach cramps, nausea, vomiting, diarrhea	Stomach cramps, nausea, vomiting, diarrhea, constipation, colic
Musculoskeletal	Muscle cramps, joint aches	Muscle cramps, joint aches, weakness, myalgias

Adapted from The Environmental Illness Resource Website

Toxicity

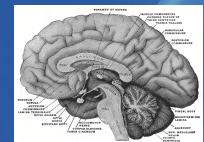
- "Neurotoxic Brainstem Impairment as Proposed Threshold Event in Autistic Regression" McGinnis WR, Miller VM, Audya T and Edelson S. CRC Press 2009
 - Intriguing phenomenon of autistic regression
 - Widely recognized in the ASD community
 - Usually presents at 18-24 months
 - Relatively rapid: days or weeks
 - Earlier problems in some children
 - Published incidences as high as 50%

Toxicity

- Features of regression
 1. **Vocalization loss**
 - Acquired words or babbling (29%/9% Lord 2004)
 2. **Social function loss**
 - At times with vocalization loss (Goldberg 2003)
 3. **Gastrointestinal Impairment**
 - (Madsen 2004; Goldberg 2004)
 - Radiographic: fecal loading or megacolon (100% Torrente 2002)
 - Reflux esophagitis (69% Horvath 1999)
 - Enterocolitis (88% Wakefield 1998, 2002)

Toxicity

- The CVO (Circumventricular organs)
 - CVO's include the
 - Pineal gland
 - Median eminence
 - Subfornical organ
 - Area postrema
 - Subcommissural organ
 - Organum vasculosum of the lamina terminalis
 - The intermediate and neural lobes of the pituitary are sometimes included.



Zonulin and Intestinal Permeability

LEAKY SMALL INTESTINE
In most people, links known as tight junctions "glue" intestinal cells together. In those with celiac disease, the junctions come apart, allowing a large amount of indigestible gluten fragments to seep into the underlying tissue and activate immune system cells. Treatments that reduce zonulin could potentially ease not only celiac disease but also other autoimmune disorders involving unusually permeable intestines.

Indigestible gluten fragment
Tight junction
Enterocyte

Zonulin and Intestinal Permeability

THE INSIDE STORY
The intestinal barrier is a complex structure that prevents harmful substances from entering the body. Zonulin is a protein that regulates the permeability of this barrier. In celiac disease, zonulin levels are elevated, leading to increased intestinal permeability and the entry of gluten fragments into the bloodstream.

Graph adapted from Scientific American August 2009

Zonulin Mechanism

The diagram illustrates the mechanism of zonulin. Zonulin binds to zonula occludens (ZO) proteins (ZO-1, ZO-2, ZO-3) on the apical surface of intestinal cells. This interaction triggers a signaling cascade involving PKC- α , F. Actin, and other molecules, ultimately leading to the phosphorylation of ZO proteins and the opening of tight junctions. This process allows for increased intestinal permeability.

Graph adapted from Fasano, 2002

New Research: Cerebral Folate Receptor Autoantibodies

- Dr. Edward Quadros- SUNY University
 - Authored papers with Dr. Vincent Ramaekers
 - Showing the presence of high affinity blocking autoantibodies to the passage of folate across the Blood-Brain barrier
 - Even though the serum folate level was normal, the CSF level was deficient, leading to cerebral folate deficiency
 - Demonstrated an inverse relationship between elevation in autoantibodies and decreased 5MTHF.

Cerebral Folate Deficiency/Folate Receptor Autoantibodies

A milk-free diet downregulates folate receptor autoimmunity in cerebral folate deficiency syndrome

Folate Receptor Alpha Defect Causes Cerebral Folate Transport Deficiency: A Treatable Neurodegenerative Disorder Associated with Disturbed Myelin Metabolism

Cerebral Folate deficiency and CNS Inflammatory markers in Alpers disease

Folate Receptor Autoimmunity and Cerebral Folate Deficiency in Low-Functioning Autism with Neurological Deficits

Autoantibodies to Folate Receptors in the Cerebral Folate Deficiency Syndrome

Blood Brain Membrane

The diagram shows the blood-brain barrier (BBB) structure. It consists of endothelial cells with tight junctions, pericytes, and astrocytes. The barrier separates the blood from the brain, preventing most substances from passing through. The diagram labels the nucleus, pericyte, lumen of the capillary, basal membrane, astrocyte, tight junction, endothelial cell, basal membrane, astrocyte, microglia, and neuron.

"A Milk-Free Diet Downregulates Folate Receptor Autoimmunity in Cerebral Folate Deficiency Syndrome"

Ramaekers J.G., Saenger J.M., Blau N., Quadros E.L. Dev. Med. & Child Neurol. (2008) 50: 344-352

- Study demonstrated a correlation in increase in folate blocking autoantibodies and milk consumption.
 - Two groups (24 total, 10 also dx with ASD) with Cerebral Folate Deficiency were split into two groups

<p>Group A:</p> <ul style="list-style-type: none"> - Baseline Folate Autoantibody testing - Folic Acid added (7 months) - test repeated - MILK-FREE diet initiated - test repeated (3-13 months) 	<p>Group B:</p> <ul style="list-style-type: none"> - Baseline Folate Autoantibody testing - Folic Acid added (7 months) - test repeated - Diet NOT CHANGED - test repeated (12-24 months)
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Results

- Introduction of Folic Acid (0.5-1.0mg/kg starting dose, adjusted to 0.4-2.5mg/kg dependent on response to therapy and CSF concentration. Continued for 7 months prior to dietary intervention.
- All participants CSF 5MTHF levels improved with folic acid supplement.
- However, the autoantibodies did not decrease.
- Significant clinical improvement in 6 out of the 10 patients with autism also observed, including improvement in regard to:
 - Attention
 - Communication
 - Less stereotypies
- This was prior to any diet change.

Results

After MILK-FREE diet introduced, autoantibodies retested from 3-13 months while pt. still on diet.

- Blocking antibodies reduced from baseline avg. of 2.08 to 0.35 (p=0.012) - 7 of the 12 on the diet had levels below detectable range.
- Of the Autistic patients, there was continued and even more significant improvement in:
 - Severe ataxia- resolved
 - Irritability, marked unrest- significantly improved

Same symptoms on pts. not on milk free diet did not see significant improvements

Cerebral Folate Deficiency and Mitochondrial Dysfunction

- Rossignol DA, Frye RE. Mitochondrial Dysfunction in Autistic Spectrum Disorders: a systematic review and meta-analysis. *Mol Psychiatry*. (2011) Jan 25 [Epub ahead of print].
 - Dr. Rossignol and Dr. Frye note that Cerebral Folate Deficiency is one of the many conditions that contribute to mitochondrial dysfunction.

Conclusion

- Research into the medical conditions associated with the DSM-IV definition of autism are headed in new and exciting directions
 - Zonulin- Mediated Tight Junction Intestinal Permeability
 - Cerebral Folate Deficiency
 - Folate Receptor Autoantibodies
 - Mitochondrial Dysfunction
- These are just a few of the new conditions being identified showing improvement with dietary interventions

Conclusion

- As these conditions are better understood, research will identify biomarkers that can then be quantified reliably.
- Treatments can then be initiated specifically toward these biomarkers and followed for progress.
- That will, in turn, improve the characteristics associated with these conditions that are defined by the checklist known as **"Autism"**

Conclusion

- Our children deserve better than a mixture of studies that are missing the target.
 - Stop measuring one intervention for a specific component of GI pathology to improving the global behaviors of autism
- In order to hit the target, however, it must be identified as such.

AUTISM IS A MEDICAL DISORDER, NOT A MENTAL DISABILITY