Gastrointestinal Issues in Children with Autism

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Conflicts

- I have no financial conflicts to disclose

GI/Autism Issues: How prevalent?

- Taylor (2002) reports chronic GI complaints in 17% of autistic children evaluated
- Fombonne 2001 cites GI complaints in an autism cohort at 18.8%
- Malloy (2003) reports 24% have chronic GI issues

GI/Autism Issues: How prevalent?

- Valicenti-McDermott, 2006, evaluated children with ASD and control groups matched for age, sex and ethnicity (50 children/group)
- 70% of children with ASD had GI Issues compared to
- 42% of children with developmental disorder other than ASD
- 28% of children with typical development

GI/Autism Issues: How prevalent?

- Vanderbilt/MGH review of the AGRE database supports high frequency of GI issues. In 460 children, 385 ASD, 75 unaffected siblings the frequency of GI complaints is 43% in ASD vs. 4% in unaffected siblings (2009)
- Schrieber and Minshew report 61% of children with ASD had GI symptoms and this correlated with affective and behavioral symptoms (2012)
- GI Issues are common and parental concerns correlate well with GI assessment. History/screening initially missed children with GI problems (Gorrindo 2012)

Food Allergy/Sensitivity

- Food allergy reported in 36% of children with autism (Lucarelli 1995)
- Up to 50% of surveyed families report their children with autism had a food allergy or sensitivity (Horvath 2002) Over 40% of children will be tried on diets.
- Higher frequency of IgE mediated food allergy to milk proteins in children with ASD compared to unaffected siblings (Trajkovski 2008)
- Sensitivity may = allergy, "drug-like" effect of food, maldigestion.

Gluten-Free Diet trials

- Knivsberg, 1990: Selected patients with high gluten opioid peptides in urine. 8/10 were reported to have behavioral improvements noted. Duplicated study in 2002
- Sponheim 1991: Selected 4 children with autism for gluten-free diet, behavior worsened
- Whiteley, 1999: Observation study of gluten free diet, 2/3 had behavioral improvements noted
- Where else? *Unraveling the Mystery of Autism*, by Karen Seroussi (Simon and Schuster, N.Y.N.Y. 2000)

Diet trials

- Elder et al* 2006 double-blind crossover trial Casein-free, Gluten-free diet in 15 autistic children showed no benefit of diet in a 12-week study
- Blinded parents reported benefits not identified by testing. Perhaps subtle changes/benefits will not be retrieved through standard tests.
- Similar trial from Susan Hyman's group in Rochester reported in abstract form

*J Autism Dev Disord. 2006 Apr;36(3):413-20

Diet trials

- MGH is currently involved in a CF GF diet trial sponsored by Nutricia evaluating the hypothesis that there are likely candidates for success with dietary restiction
- Enrollment is based on gastrointestinal symptoms for inclusion, hopeful that this subset may be more likely responders.
- A remarkable allergy work-up is part of this study to try to identify markers supporting the rationale, although other mechanisms of intolerance or flora modulation may be at play

Autism/GI Issues

- Lactose intolerance and other carbohydrate digestion problems reported by Horvath (1999) and Kushak (2010)
- Our recent data (published in Autism, 2010) suggests high frequency of lactase deficiency in autistic children undergoing endoscopy for GI symptoms, BUT comparison group has a high frequency as well.

Autism/GI Issues
Inflammatory Bowel Issues

- Wakefield (1998) identified a group of autistic children with GI issues.
  - At colonoscopy, *lymphoid nodular hyperplasia* (7 of 12) in the distal ileum and frank colitis in 11 of 12 patients identified. This paper was retracted from Lancet
  - Wakefield 2000 describes "*autistic enterocolitis*" as a unique intestinal lesion with prominent LNH and colitis
- Walker 2013 discusses the findings of gene expression differences in children with ASD and inflammatory bowel diseases compared to non-inflamed individuals. Some distinct difference were seen in children with ASD and IBD although overlap is seen

Thoughts on the GI Literature

- In May 2008, a consensus meeting of experts was brought to Boston in an attempt to review and vet the quality of the literature and research regarding Autism and GI issues Sponsored by Easter Seals of Oregon, The Autism Society (of America), The Autism Research Institute
- The resulting consensus papers have been published in Pediatrics, 23 consensus statements issued by 27 experts
- http://pediatrics.aappublications.org/cgi/content/full/125/Supplement_1/S1
- http://pediatrics.aappublications.org/cgi/content/full/125/Supplement_1/S19

Evaluation, Diagnosis, and Treatment of Gastrointestinal Disorders in Individuals With Autism Spectrum Disorders: A Consensus Report

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

Evaluation, Diagnosis, and Treatment of Gastrointestinal Disorders in Individuals With ASDs: A Consensus Report
T. Buie et al, Pediatrics 2010; 125: S1-S18

Evaluation, Diagnosis, and Treatment of Gastrointestinal Disorders in Individuals With Autism Spectrum Disorders: A Consensus Report

- **Statement 2:** GI conditions reported to be common in individuals without ASDs are also encountered in individuals with ASDs.
- **Statement 3:** The prevalence of GI abnormalities in ASDs is incompletely understood.
- **Statement 4:** The existence of a GI disturbance specific to persons with ASDs (e.g., "autistic enterocolitis") has not been established.

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Evaluation, Diagnosis, and Treatment of Gastrointestinal Disorders in Individuals With Autism Spectrum Disorders: A Consensus Report

- **Statement 6:** Individuals with ASDs and GI symptoms are at risk for problem behaviors. When patients with GI disorders present with behavioral manifestations, the diagnostic evaluation can be complex.
- **Statement 8:** Education of caregivers and health care providers is necessary to impart knowledge of how to recognize typical and atypical signs and symptoms of GI disorders in individuals with ASDs.

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Unsettled Issues

Could GI issues CAUSE autism?

- Environmental/nutritional/microbiome associated factors modulating genetically predisposed individuals

- An inflammation model where some body process (colitis, allergy, infection) releases chemical or immune mediators that affect brain function (Vargas 2005, Welch 2005)

New Thoughts

- Bacterial flora disruptions may alter behavior
- Bacterial flora disruptions exist in the autism population
- There are a number of pathways potentially accounting for altered pain sensitivity, emotional stability etc from this dysbiosis
- Diet changes may alter bacterial flora
- Animal models have been developed to suggest an autism-like change

GI Symptoms in ASD and MET Gene Is MET polymorphism a biomarker?

- A genetic variant that disrupts MET transcription is associated with autism (Chromosome 7q31 polymorphism G>C) Proc Natl Acad Sci U S A. 2006 Nov 7;103(45):16621-2. Campbell et al;
- Distinct Genetic Risk Based on Association of MET in Families with Co-Occurring Autism and Gastrointestinal Conditions (Pediatrics 2009;123;1018-1024; Campbell et al)
- A known affect of this gene abnormality is poor intestinal healing, newer studies suggest autoimmune relationship in mothers with abnormality (Heuer 2011)

Impaired CHO Digestion and Transport and Dysbiosis

- In AUT-GI subjects, ileal transcripts for the disaccharidases sucrase isomaltase, maltase glucoamylase, and lactase, and the monosaccharide transporters, sodium-dependent glucose co-transporter, and glucose transporter 2 were significantly decreased. (Williams et al, PLOS One Sept 2010)

Impaired CHO Digestion and Transport and Dysbiosis

- This study supports our previous enzymatic findings of disaccharide deficiency and goes further to show associated flora alteration is present (cause/effect?)
- This supports rational for overgrowth syndrome (so called dysbiosis)

Abnormal Microbiome Assessments

- Feingold: Desulfovibrio species identified in ASD sources, not in control comparisons (Anaerobe 2010)
- Williams: Sutterella species identified in children with ASD but not controls (PLOS 2012)

Conclusions

- GI issues are common in children with autism and some may be more common than in the general pediatric population
- GI conditions in autism may promote worsening of autistic behaviors, more work is needed to determine if any impact on causation of autism
- The GI tract is accessible for study and may be a valuable (if messy) window to the body for genetic, microbiota and inflammatory mediator data

Conclusions

- The pediatrician needs to consider the child with autism in a medical light
- Until proven otherwise, behaviors should be considered medically-based. Testing and treatment algorithms are crucial so as not to put this vulnerable population at risk for excessive testing or unnecessary treatment
- Profound aggression or self injurious behaviors may require psycho-pharmacological or behavioral management to stabilize the patient. Attention to the possible medical etiology should be pursued as well