

Gastrointestinal (GI) & Nutritional Problems in Children with ASD

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Disclosure

I do not have any conflicts of interest or financial relationships with commercial interests relevant to this presentation.

There are no relationships to disclose.

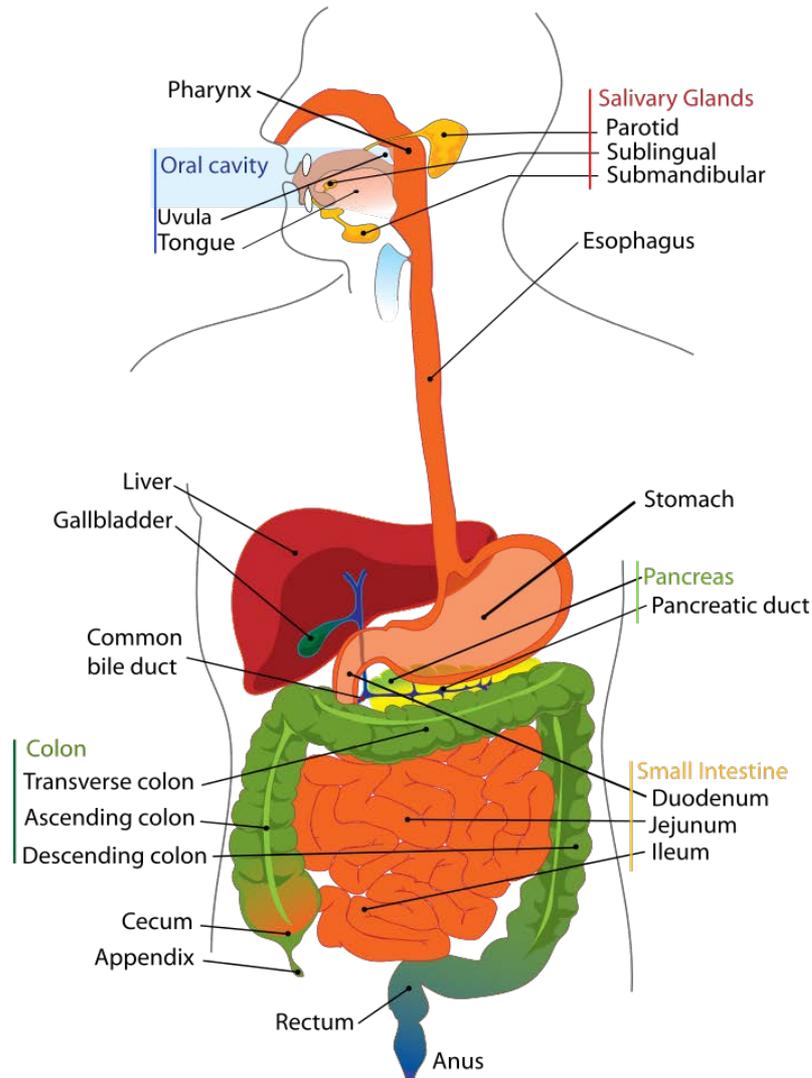
Objectives

- To discuss common GI problems in children with ASD.
- To discuss some approaches to evaluation and treatment of common concerns.
- To briefly discuss some of the theories about the relationship of ASD to the GI tract.

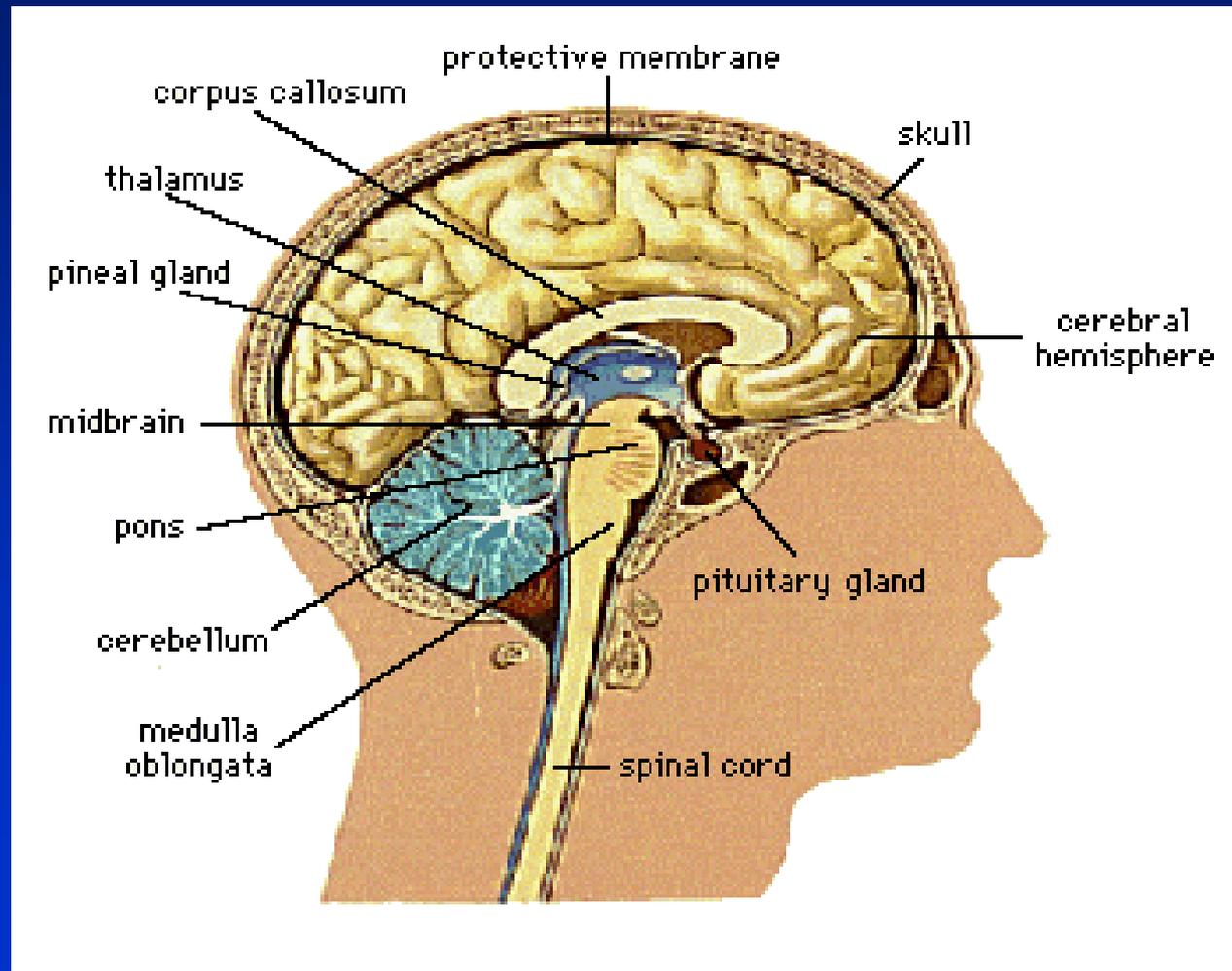
Categorization & Questions

- GI problems
- Feeding problems
- Nutritional problems
- Relationship of GI problems to underlying cause of ASD/DD
- Dietary intervention in children with ASD

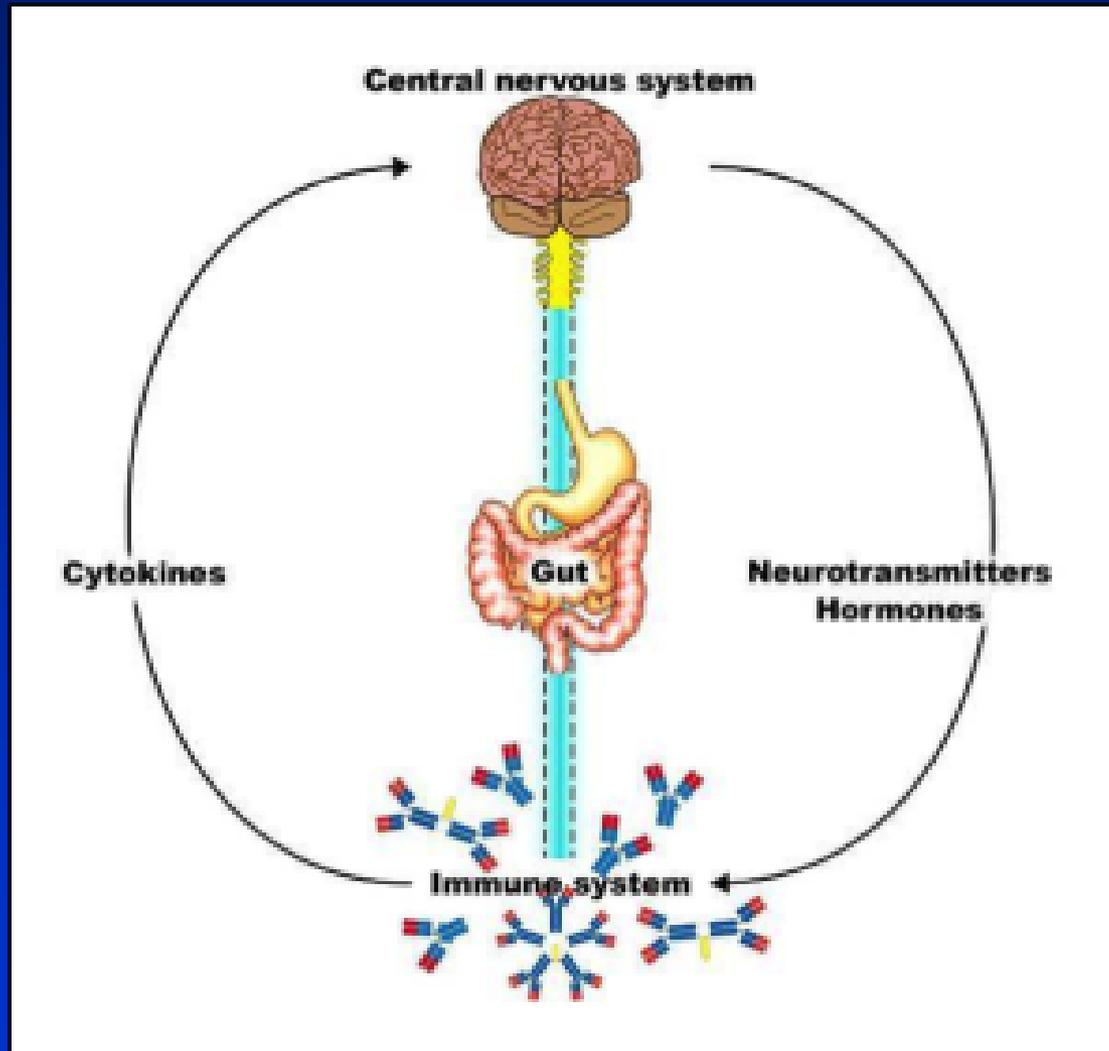
The Digestive System (GI Tract)



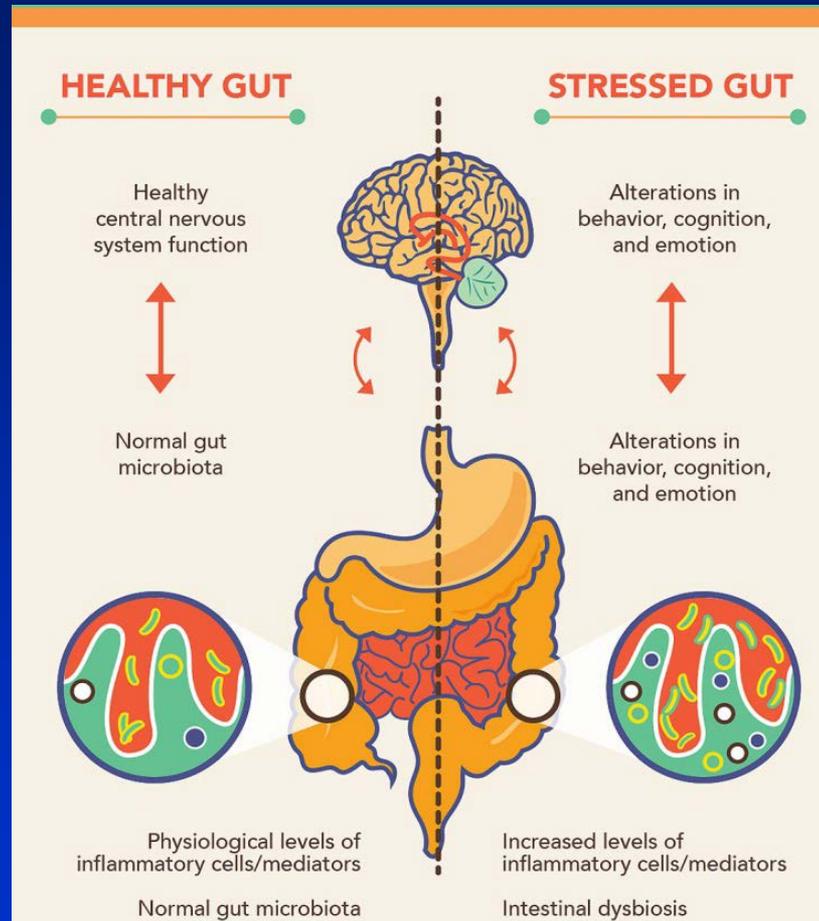
The Brain



Connection?

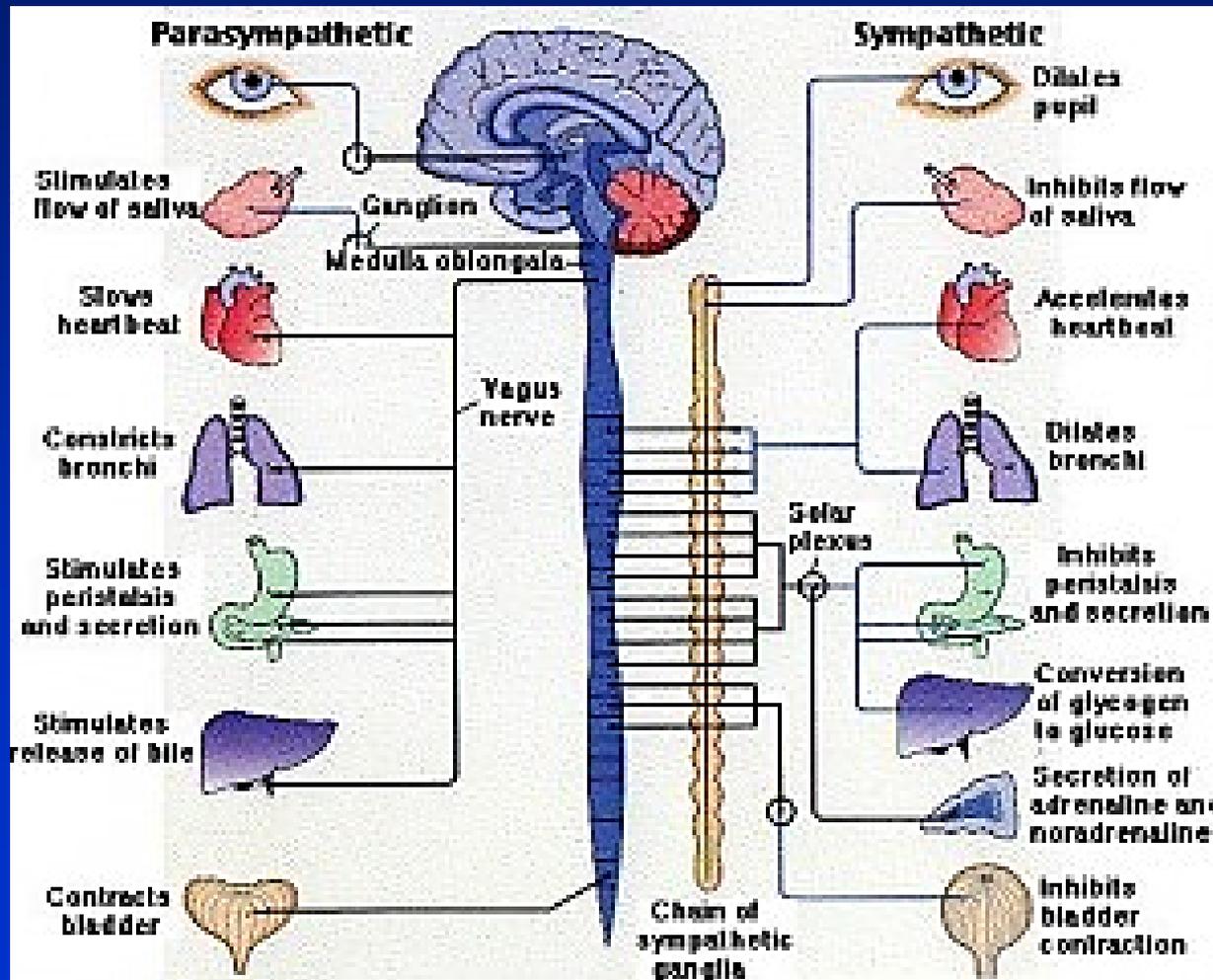


The Gut-Brain Connection



A stable and healthy gut is essential to overall health. Intestinal dysbiosis, or an imbalance, can negatively influence the gut and the brain.

Brain & Autonomic Nervous System



GI Problems are Common in Children with ASD

- GI disorders and associated symptoms are commonly reported in individuals with ASD
 - In recent meta-analysis, children with ASD > 4x likely as typically developing peers to have GI problems such as abdominal pain, diarrhea, or constipation.
[McElhanon BO, Pediatrics 2014]
 - In a recent study of children with ASD seen in a clinical setting, 49% were reported to have one or more GI complaints
[Kang, Autism Research, 2014]
 - 26% had constipation and 22% exhibited diarrhea
 - 13% bloating / gassy
 - 10% vomiting / gastroesophageal reflux
- Accurate prevalence not established
- Communication difficulties make recognizing and characterizing symptoms challenging

Most Common GI Problems

- Chronic constipation
- Chronic diarrhea
- Abdominal pain
- Bloating, excessive gas
- Vomiting, gastroesophageal reflux

These are often functional disorders

Possible Causes of GI Problems

- Abnormal diet due to food selectivity/preferences
- Exaggerated sensory response
- Behavioral factors
- Medications
- Underlying GI conditions that are seen in general population such as Celiac Disease, food allergies or intolerances
- Neurenteric dysregulation (abnormal nervous system regulation of GI tract)
- Genetic factors that contribute to ASD and GI problems
- Mitochondrial dysfunction
- Underlying intrinsic abnormality of GI tract (increased permeability or inflammation, altered gut microbiome) that contributes to development of ASD

Feeding Problems are Common in Children with ASD

- In Kanner's first description of ASD in 1943, he described feeding problems in 6 of 11 patients
- A 2006 review of feeding problems in children with ASD by Ledford & Gast, found 7 quantitative descriptive studies and 9 experimental intervention studies
 - All descriptive studies found evidence of substantial feeding problems in children with ASD
 - Problem feeding behaviors in 46 to 89% of children with ASD
- A 2010 review, evaluated food selectivity and studies of dietary intake and nutritional status in ASD (Cermak)
 - Found significant food selectivity in ASD
 - Studies of nutritional status were inconclusive
- More recent meta-analysis (Sharp, 2013)
 - 17 prospective studies involving a comparison group
 - All studies reported greater levels of feeding concerns for ASD relative to the comparison group
 - Children with ASD had significantly more feeding problems versus peers, OR 5.11 (5 times risk of TD children)

Types of Feeding Problems in Children with ASD

- Feeding problems often not well-defined in studies
- Food selectivity or selective eating (picky eating)
 - preferences or aversions to food based on texture, color, taste, smell, temperature, shape, or categories of food
 - Often rigidity with respect to specific brand of food or color and packaging of food
- Food refusal behaviors (general or specific)
- Other difficult mealtime behaviors
- Limited variety (decreased food repertoire)
- Restricted intake or poor appetite (limited volume or calories)
- Delayed feeding skills (self-feeding, chewing)
- Dysphagia – difficulty chewing and swallowing
- Over-eating
- Eating too quickly
- Pica

Problem Behaviors

Food Refusal

- Turns head
- Expels food / spits
- Overstuffs mouth
- Packs food
- Crying
- Tantrums or acts out
- Gagging, choking, or coughing with feeds
- Vomiting

Other Problem Behaviors

- Refuses to come to the table
- Refuses to sit at the table
- Throws food
- Argues
- Seeks attention
- Squirms or fidgets

Feeding Problems of Patients with ASD seen in a Feeding Clinic

- Study of children in an interdisciplinary feeding clinic (Field, 2003). Types of feeding problems in ASD
 - 62% selectivity by type of food
 - 31% selectivity by texture
 - 15% oral-motor delays (mechanical difficulties eating foods, including chewing, moving the tongue, or closing the mouth)
 - 12% dysphagia (difficulty swallow foods)
 - 12% food refusal (not consuming sufficient calories or satisfying nutritional needs)

Factors contributing to Food Selectivity in ASD

- Core features of ASD such as restricted interests, rigidity, neophobia
- Sensory issues
 - Hypersensitivity (e.g. oral aversion, defensiveness)
 - Hyposensitivity (preference for crunchy foods)
- Delayed feeding skills
- Extreme behaviors and response of caregivers (reinforcement of maladaptive behaviors)
- GI and other medical conditions

Feeding Disorders Clinic

- 8 yo with ASD & overweight. Eats only chicken nuggets, goldfish, Cheez-Its and McDonald's French fries. Drinks milk. Eats no fruits or vegetables.
- 2 yo with ASD & underweight. Difficulty advancing from puree. Limited self-feeding and chewing. Started eliminating foods.
- 6 yo with ASD & nl weight. Baby bottle dependent. Little variety.
- 7 yo with ASD & eosinophilic esophagitis. G-tube dependent on Elecare. Difficulty introducing table foods that are considered safe.
- 5 yo with ASD & underweight. Meal duration is 1 to 2 hours. Difficult mealtime and other behaviors. High parent stress and anxiety.
- 10 yo with ASD, profound ID, limited repertoire of foods. On GF/CF diet, methyl-B12 injections, pancreatic enzymes, omega-3 fatty acids (fish oil), and probiotics.

Consequences of Food Selectivity in ASD

- Inadequate or excessive caloric intake
- Inadequate or excessive intake of specific nutrients
- Effects on growth and development
 - Underweight
 - Overweight
 - Poor growth / failure to thrive
- Effects on health (not well-documented)
- Effects on behavior
- Dependence on tube feeding
- Negative parent / child interaction
- Parent stress / family dysfunction
- Financial cost

Treatment of Food Selectivity and Feeding Problems in Children with ASD

- Therapy often done by Speech-Language Pathologists (SLP), Occupational Therapists (OT), or Behavioral Therapists (BT)
- Behavioral therapy is typically based on operant conditioning or systematic desensitization
- Few studies of SLP or OT techniques
- Most of the peer-reviewed, scientific studies are of behavioral intervention
- Ledford & Gast 2006 reported on 9 intervention studies published from 1994-2004
 - Very small studies (n=1 to 6)
 - All showed successful treatment
 - Variety of behavioral techniques including
 - Simultaneous presentation
 - Sequential presentation
 - Differential reinforcement
 - Stimulus fading
 - Escape extinction
 - Appetite manipulation
- More recent review of 23 studies Jan 2000 – Oct 2013 (Marshall, 2014)
 - Challenges to research in terms of definitions of population, intervention, target outcome variables, measurement
 - Most showed increase in desirable behaviors

Interdisciplinary Feeding Programs

- Interdisciplinary treatment team (KKI and others)
 - Behavioral treatment
 - OT, SLP
 - Nutrition
 - GI and/or Pediatrics
- Outpatient therapy versus intensive therapy
- A retrospective review of outcomes of children with ASD in the KKI program was published in 2009 (Laud et al., 2009)
 - 46 children with ASD
 - Behavioral treatments included
 - Differential reinforcement
 - Escape extinction
 - The Premack principle
 - Textural manipulation
 - Measures of eating problems improved on the Children's Eating Behavior Inventory (CEBI)
 - Average caregiver satisfaction was very to extremely satisfied
 - Improvements tended to be sustained over time (follow-up at 1 or 3 years)
- A review and meta-analysis of intensive multidisciplinary feeding programs published in 2016 (Sharp et al.) demonstrated efficacy.

Functional Abdominal Pain or Irritable Bowel Syndrome

Could present with:

- Behavioral indicators of pain
- Disordered sleep
- Diarrhea
- Constipation
- Bloating
- Flatulence

Could be due to neurenteric dysregulation

Behavioral Indicators of Pain or Discomfort

- **Vocal behaviors:**

- Clearing of throat, swallowing, tics
- Screaming, sobbing, sighing, whining, moaning, groaning
- Delayed echolalia that includes reference to pain or stomach
- Direct verbalizations, eg, “tummy hurts”

- **Motor behaviors:**

- Facial grimacing, gritting teeth, wincing
- Constant eating/drinking/swallowing (grazing behavior)
- Application of pressure to abdomen
- Tapping behavior or finger tapping on throat
- Unusual posturing: jaw thrust, neck torsion, arching of back, odd arm position, abdominal sensitivity/flinching
- Agitation: pacing, jumping up and down
- Unexplained increase in repetitive behavior
- Self-injurious behaviors: biting, hitting/slapping face, head-banging
- Aggression: onset of, or increase in, aggressive behavior

- **Changes in overall state:**

- Sleep disturbance
- Increased irritability (exaggerated responses to stimulation)
- Noncompliance with demands that typically elicit an appropriate response (increased oppositional behavior)

Findings that May Prompt Further Evaluation

- Weight loss or growth stunting
- Blood in the stool
- Fever (unexplained)
- Persistent vomiting
- Persistence/duration of symptoms and severity
- Anemia
- Laboratory markers of inflammation
- Family history (especially of inflammatory bowel disease)
- Abnormal physical findings

Empiric Treatment

- Abdominal pain/GERD: Trial of proton pump inhibitor (PPI) for 2 to 4 weeks
 - ex. Prevacid (lansoprazole), Prilosec (omeprazole)
- Abdominal pain/Constipation: Trial of Miralax (polyethylene glycol) for 4 weeks
- Abdominal pain/Gas: Trial of lactose-free diet for 2 weeks

Diagnostic Considerations

- Radiology:
 - X-ray of abdomen to assess constipation
 - Upper GI series to assess anatomy/function
- Stool studies
 - Infectious: enteric pathogens, ova/parasites, Giardia, C. Diff toxin
 - Inflammation: blood, calprotectin, lactoferrin
 - Malabsorption: fecal fat, α -1-antitrypsin
- Blood tests:
 - CBC to look for anemia, iron deficiency, white blood cell count
 - Markers of inflammation: CRP, ESR
 - Other markers of nutritional status: protein, albumin, vitamin D
 - Markers of liver disease, pancreatic disease
 - Serologic testing: gluten-sensitive enteropathy, food allergies
- Endoscopy: upper endoscopy (EGD), colonoscopy

Suspected Malabsorption (maldigestion)

- Symptoms include diarrhea, excessive gas, bloating
- Could lead to poor weight gain
- Consider upper endoscopy with measurement of disaccharidases
- Lactose intolerance is common in general population, so consider
 - Lactase supplementation
 - Dietary restriction of lactose

Nutritional Intake of Children with ASD

- Studies of dietary intakes of children with ASD show they are similar to American children in general
- About 80% have insufficient intake of Vitamin D
- Tend to lower than recommended intakes of Vitamin A, **D**, **K**, **calcium**, magnesium, phosphorus, potassium, choline, and fiber
- Tend to have sufficient intake of iron, vitamin B6, B12, and folate

[Hyman, Pediatrics, 2012]

Symptomatic Nutrient Deficiencies are Rare

- Reports in Children with ASD
 - Rickets – due to vitamin D deficiency (Stewart, 2008)
 - Scurvy – due to vitamin C deficiency (Niwa, 2012)
 - Visual impairment – due to vitamin A deficiency (Tanoue, 2011)
 - Optic neuropathy – due to vitamin B12 deficiency (Pineles, 2010)
 - Anemia, rash, edema/hypoproteinemia – due to iron and zinc deficiencies as well as inadequate protein intake (Tang, 2011)
- No deficiency that is common in children with ASD or that explains ASD symptoms
- Cases are due to extreme diets that are highly selective
- Subsets of children with severe food selectivity are at some risk for specific nutrient deficiencies depending on the composition of their diet

Are there intrinsic problems with intestinal function in children with ASD?

- Some studies have been provocative
- In 1996, D'Eufemia reported increased intestinal permeability in ASD
- In 1999, Horvath reported on 36 children with autistic disorder who had EGD due to GI complaints including chronic diarrhea, gaseousness, abdominal discomfort and distension
 - 69% had reflux esophagitis
 - 42% chronic gastritis
 - 67% chronic duodenitis
 - 58% low intestinal carbohydrate digestive enzyme activity
 - 75% increased pancreato-biliary fluid output after IV secretin administration
- Raised possibility of unrecognized GI disorders and the possibility that GI inflammation in ASD may be common
- More recent studies show children with ASD who have GI symptoms have similar findings to children without ASD (Kushak, 2016)
 - Compared 61 children with ASD and GI symptoms to 50 children with GI symptoms and without ASD
 - Evaluated biopsies for inflammation, disaccharidase activity, intestinal permeability, and fecal biomarkers of inflammation

Theories about Relationship of GI Tract to ASD

- Role of intestinal inflammation
 - Auto-antibodies
 - Pro-inflammatory cytokines
 - Food allergies / intolerances (elimination of foods)
- Increased intestinal permeability / mucosal disruption
 - Passage of opioid or other peptides (justification for GF/CF diet)
 - Decreased absorption of vitamin B12 (justification for methyl-B12)
 - Failure to detoxify (justification of other supplements)
- Altered gut microbiome / dysbiosis (clostridia, yeast)
 - Possible benefit of antibiotics (vancomycin)
 - Possible role for probiotics
 - Dietary modification could change intestinal flora
- Immune dysregulation / altered immune response
 - Could lead to immune reactivity to common dietary proteins
 - Special diets or supplements (fatty acids) may lower immune activation
- Role of processed foods as toxins
 - Artificial sweeteners (aspartame), artificial flavors and colors
 - Fructose (e.g. high fructose corn syrup)
 - Advanced glycation end products
- Role of oxidative stress and mitochondrial dysfunction
 - Possible benefit from anti-oxidants or diets high in anti-oxidants
- Role of excitotoxicity (glutamates and aspartates)
 - Possible benefit from elimination diet (eliminate MSG and aspartame)

Theories about Relationship of GI Tract to ASD

- Increased gut permeability (“leaky gut”)
 - Hypothesis that peptides from foods crossed leaky gut and are absorbed into bloodstream and have effects on the brain
 - Was theory that supported use of gluten-free, casein-free diet
 - Increased intestinal permeability was reported in 9 of 21 (43%) of autistic patients and 0 of 40 controls (D’Eufemia, 1996)
 - Has not been replicated and theory is losing favor (Kushak, 2016)
- GI inflammation may have a role in pathogenesis of ASD
 - Association between ileocolitis and developmental regression
 - Wakefield in 1998 reported association in 12 children and called it “autistic enterocolitis”
 - No control group. These findings are common in normal children.
 - He has since been discredited.
 - High rates of inflammation seen in a population being referred for upper endoscopy (Horvath, 1999) – no control group

More Theories

- Altered Gut Microbiome / Dysbiosis
 - Expanding body of research showing importance of intestinal flora and impact on health, e.g. allergy, asthma
 - Several studies have reported abnormalities in microbiota composition and differences in microbial metabolites in children with ASD
 - No treatment studies

Dietary Supplements in Children with ASD

- Many children with ASD are given nutritional or dietary supplements
 - Stewart, 2015 – 56%
- Even with supplementation, many children with ASD still have inadequate intake of some nutrients, i.e calcium & vitamin D
- With supplements, some children are receiving excess amounts of vitamin A, folic acid, and zinc
- For younger children, also excess copper

Specific Diets

- Gluten-Free / Casein-Free Diet
- Specific Carbohydrate Diet
- Body Ecology Diet
- Feingold and Failsafe Diets
- Raw food diets
- Antioxidant diets
- Ketogenic Diet
- Other Elimination Diets to avoid allergens or toxins
 - Identification of allergens by skins tests or IgE testing
 - Less accepted IgG or IgA tests, patch testing
 - Elimination of additives, preservatives, or artificial sweeteners
 - Other
 - Sugar free
 - Caffeine free
 - Yeast free

Other Dietary Interventions

- Ketogenic diet – trend to benefit [Castro 2015]
- Low glycemic index diet
- Omega-3 fatty acids – Cochrane evaluation 2011, insufficient evidence
- Anti-oxidants
- Vitamin B12, methylcyanocobalamin, and folic acid

Dietary Intervention

- Nothing proven to work
- Most common is gluten-free, casein-free diet
 - Recent double-blind, placebo controlled study showed no benefit

[Hyman et al, J Autism Dev Disord (2016) 46:205–220]
- Other Elimination Diets to avoid allergens or toxins
 - No additives or preservatives, sugar free, yeast free, caffeine free
- Digestive enzymes or pancreatic enzymes
 - A randomized controlled trial show no improvement in ASD symptoms, but some improvement in food variety
 - Some children may have exocrine pancreatic insufficiency

Consensus Report

- Evaluation, Diagnosis and Treatment of Gastrointestinal Disorders in Individuals with ASDs: A Consensus Report
[Buie T et al. Pediatrics 2010;125:S1-S18]
- Consensus opinion of the panel was that evidence-based recommendations cannot be made, yet.
- **#1** Individuals with ASD deserve the same thoroughness and standard of care in the diagnostic workup and treatment of gastrointestinal concerns as should occur for patients without ASD.
- **#2** GI conditions are commonly reported in individuals with ASD.
 - GI conditions that commonly reported in individuals with ASD include chronic constipation, abdominal pain, diarrhea, encopresis.
- **#3** Prevalence of GI conditions in individuals with ASD is incompletely understood.
- **#4** The existence of a GI disturbance specific to persons with ASDs has not been established.

Consensus Statements Continued

- **#5** Evidence for abnormal GI permeability is limited.
- **#6** Individuals with ASDs and GI symptoms are at risk for problem behaviors.
- **#7** For a person with ASD and problem behavior, should consider possibility that GI symptom is precipitating factor.
- **#8** Education of caregivers and health care providers is necessary, including knowledge of how to recognize signs and symptoms.
- **#9** Pediatricians and other primary care providers should be alert to potential nutritional problems.
- **#10** Primary care nutritional assessment should include weight for height or BMI, weight for age, height for age, and any marked changes in growth rate.
- **#11** There may be a subgroup of individuals with ASD who respond to dietary intervention.

Consensus Statements Continued

- **#12** Available research does not support the use of casein-free diet, a gluten-free diet, or a combined gluten-free, casein-free diet as primary treatment for ASD.
- **#13** For patients with ASD, a detailed history should be obtained to identify potential associations between allergen exposure and GI and/or behavioral symptoms.
- **#14** Standardized definitions of adverse reactions to foods would be helpful.
- **#15** A detailed history and physical exam should be performed to accurately identify potential comorbid allergic disease.
- **#16** Involvement of specialists such as allergists, gastroenterologists, dietitians, and feeding therapists may be beneficial
- **#17** Immunologic aberrations in individuals with ASD have been reported, however, a direct cause-and-effect relationship between immune dysfunction and ASDs has yet to be proven

Consensus Statements Continued

- **#18** The role of immune responses in the pathogenesis of GI disorders in ASD warrants additional investigation.
- **#19** The role of gut microflora in the pathogenesis of GI disorders in ASD is not well understood.
- **#20** It is imperative that the phenotype of study subjects be well defined in future studies.
- **#21** Studies of GI disorders in ASD should include genetic testing of all participants
- **#22** Prevalence and characterization of specific GI symptoms should be examined in well-defined genetic syndromes with high rates of ASD
- **#23** Clinical trials of treatment of GI symptoms should include banking of DNA samples

Thoughts?

- There is no one cause of ASD
- There may be subsets of children with ASD who have certain deficiencies or problems, while most do not
- We may find that some children with ASD respond to GFCF diet, while most do not
- Proposed treatments may work for a small subset
- For example, a minority of children with ASD likely have a mitochondrial disorder and may respond
- If you try something:
 - Do one trial at a time
 - Do no harm
 - What symptoms are you targeting?
 - Do baseline measurement and measurement during treatment
 - Make some assessment of effectiveness and adverse effects

Thank You!

Questions?

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