Gastrointestinal Problems in Children with Autism: Recognition of the problem and a potential link with serotonin

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My Roles in Autism

- Pediatric Gastroenterologist at Columbia
  - Kids with ASD and Gastrointestinal (GI) issues
- Physician-scientist
  - "The second brain": enteric nervous system
  - Roles of enteric nervous system development: serotonin and oxytocin
  - Motor disorders (how well the intestine moves)
- Gastrointestinal and clinical/translational
  - GI motility
- GI of ASD

Objectives

- GI Conditions in Autism
  - Prevalence
  - Types
  - Presentations
- Serotonin as a link between the brain and intestinal abnormalities in ASD

History of GI Issues in ASD

- 1943: Leo Kanner described autism in his seminal paper
  - 7/11 children described to have "feeding or dietary issues"
  - Supportive of association between ASD & GI problems
- These issues all related to autistic behavior
  - A theme throughout history

Gastrointestinal disorders are more common in children with ASD

- 9.9%/98
- High rate of GI disorders in children with ASDs
- ASDs >> typical
- All but one study
- Multicenter retrospective prevalence study
- 74600 individuals
- Age 7
- 2–3x more common

GI symptoms are common in autistic spectrum disorder (ASD)

- Meta-analysis confirms reason for this concern.
  - Overall: OR 4.42
    - 95% CI, 1.90–10.28
  - Constipation: OR 3.86
    - 95% CI, 2.23–6.71
  - Diarrhea OR 3.63
    - 95% CI, 1.82–7.23

B McElhanon et al. Pediatrics 2014;133;872

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GI problems are common in ASD

- Motility abnormalities:
  - 3.5x more common than normally developing peers\(^1\)
  - Constipation
  - Diarrhea
- Abdominal pain:
  - Gastro-esophageal reflux disease (GERD)
  - Esophagitis, gastritis, duodenitis
- Others:
  - Nutrition
  - Food/allergy/texture aversion
  - Dysbiosis (small bowel bacterial overgrowth)
  - Inflammatory bowel disease\(^12\)

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0.83% versus 0.54%\(^{1,2}\)


Gastrointestinal Symptoms cause difficult behaviors

- Intensity correlates with behavior severity
- Comorbidities can arise as a result of GI discomfort\(^1\)
  - Irritability
  - Anxiety
  - Social withdrawal
  - Regression
  - Sleep disturbance
  - Pica

Presentation of GI pain in ASD\(^2\)

- Abnormal posturing
- Self-injury to the abdomen or other areas
- Head banging, rocking
- Vocal groaning or screaming
- Aggression
- Verbal fits

GI problems are significantly associated with specific behaviors in ASDs\(^7\)

- Self-injury, aggression, self-mutilation
- Limited interpersonal behaviors
- Sleep disturbances, impulsive, seeming or erratic
- Irritability, difficulty with change
- GERD, gastritis and overall GI problems

Self-injurious behaviors improved with treatment with an acid blocker

From files of Tim Buie, MD
Joanna: Sandifer syndrome

• Usually in infants/toddlers
  – Adolescence in children with developmental disorders
    • nodding and rotation of the head
    • neck extension
    • gurgling
    • writhing movements of the limbs
    • severe hypotonia
• Joanna’s diagnoses:
  • GERD
  • Erosive esophagitis despite standard PPI dosing
• Behaviors eliminated with bid dosing of PPI and sucralfate

A brain-gut connection in ASD

• GI problems may result from genetic and/or environmental risk factors for ASD
  – Stratify subpopulations of individuals
• Environmental
  – Maternal inflammation
  – Intestinal microbiome
• Genetic
  – C-met
  – CHD8
  – SERT G56A

Conclusions

• GI issues are common in children with autism
  • prospective, population-based studies needed to confirm whether GI problems are more prevalent in subsets of ASD
• GI conditions in autism may worsen behaviors and other co-morbidities
  • GI conditions should be ruled out
  • Critically needed:
    • Testing and treatment algorithms
    • Cause & effect studies
• Aggression or self-injurious behaviors may require psychopharmacological or behavioral management
  • Medical etiologies should also be evaluated

A brain-gut connection in ASD: emerging research in environmental risks

• maternal immune activation
  – Inflammation is a potential non-genetic cause of autism
  – epidemiological studies link-maternal infections & elevated pro-inflammatory markers to increased autism risk in offspring
  – Mouse models of maternal immune activation
  – ASD-related behavioral aberrations, intestinal immune and inflammation and increased intestinal permeability
• Mice are not people
  – Unknown whether there is an increased prevalence of GI conditions in this population

Etiology of GI Problems in ASD

• Medications
  • Selective Serotonin Reuptake Inhibitors:
    – Paxil, Prozac
      – Abdominal pain, nausea, gastritis, ulcers, GI bleed
      – Diarrhea → constipation
      – Decreased → increased appetite
  • Antipsychotics:
    • Increased appetite
    • Constipation
• Supplements
  • Probiotics: bloating, nausea, cramping
  • Fish oil: nausea, abdominal cramping
  • appropriate dosing
  • trial without supplements

A brain-gut connection in ASD: microbiome

• Gut microbiota
  – Ensemble of microorganisms that reside in the intestine
  – contains trillions of microorganisms
  – >1000 different species of known bacteria
  – up to 4 points
  – >3 million genes
  – 150% more than human genome
  – like an individual identity card
  – 2/3 common to most people
  – 2/3 are specific to individuals
  – Affected by many factors
• Why is the gut microbiota so important?
  – Directly impacts on our health
    • Helps to digest certain foods
    • Vitamin production (B and K)
    • Helps to combat aggression from “bad” or harmful bacteria
    • Helps to preserve gut permeability
• Microbiome alterations may alter behavior 4,5:
  - germ-free mice inoculated with selective bacteria alter anxiety/depressive behaviors.
• Altered composition of the intestinal microbiota in ASD 1-8:
  - Desulfovibrio species in exclusively ASD
  - Sutterella species in kids with ASD & GI comorbidities.
• Intestinal Consequences of altered microbiota:
  - Impaired carbohydrate digestion 1-5
  - Metabolite differences
• Future of microbiome research:
  - Which gut bacteria make a difference?
  - Function
  - Role of the metabolome
  - Is GI the chicken?

**A brain-gut connection in ASD: microbiome**

**A brain-gut connection in ASD: Genetic risk factors**

- C-met
- CHD8
- SERT G56A

**Disruptive CHD8 Mutations Define a Subtype of Autism in Early Development**

- Chromodomain Helicase DNA Binding Protein 8
  - spina bifida
  - pentalogy of fama
  - First gene mutation to show a very strong penetrance linked to a subtype of autism
  - First direct relationship between a gene mutation & ASD
  - 5,176 children with ASD
  - SS had a CHD8 mutation
  - all had similar characteristics in appearance
  - Large MYH18 and TBC1D8A mutations
  - Interfaced families of all cases with CHD8 mutations
  - Deep dysregulation & gastrointestinal problems
  - To confirm the findings, researchers disrupted the CHD8 gene in zebrafish
    - developed large heads & wide set eyes
    - fish had fewer intercranial and perinatal problems
    - ASD symptoms displayed on behavior
  - Results could lead to a “genetics-first approach”
  - Short-term, medications can provide targeted treatment

**A Brain-Gut Connection in Autism: Serotonin**

- 3%
- 95% !!!!
Serotonin, Autism & the Brain

- Serotonin important for pre- and postnatal human brain development
  - Abnormal brain serotonin levels → abnormal connecting neural circuits
  - Changes in serotonergic function & signaling associated with ASD
    - Increased in serotonin stores branching in temporal cortex
    - Associated with auditory sensation & language

- Humans undergo high brain-serotonin synthesis capacity during childhood
  - Functional neuro-imaging studies (PET scan) show diminished serotonin synthesis

Serotonin is Critical for Gut Function!

- Intestine
  - 95% of the body’s serotonin is located in the intestines!
  - Critical mediator
    - Enteric nervous system development
      - Brain to the gut
      - Control many functions
    - Intestinal motility
      - How fast, slow or coordinated gut movement is
    - Intestinal secretion
      -flush that make stool softer

Intestinal Serotonin Mechanics

- TPH1 = produces mucosal serotonin
- TPH2 = produces neuronal serotonin
- SERT = inactivation of serotonin

Manipulation of serotonin homeostasis alters neuroanatomy & functions of the intestine......

How do we put this all together?

- Is disruption in serotonin homeostasis a cause of both brain and gut abnormalities in ASD?
  - Abnormality in the serotonin transporter (SERT)
- Genome-wide association study for SERT-associated genetic abnormalities in ASD
- Several SERT coding variants identified as risk factors in children with ASD
  - All result in overactive serotonin transporter activity
  - Take up (inactivate) serotonin with increased efficacy
- Most common coding variant: G56A
  - G56A transgenic mouse
  - SuperSERT mouse

GI problems are common in children with autism: Is 5-HT the Link?
SERT G56A ("SuperSERT") Transgenic Mouse

- Expresses the most common gain-of-function SERT coding variant in children with ASD
  - Core autism-related behavioral abnormalities
    - Altered social function & communication, repetitive behaviors
  - High blood serotonin levels
    - 30% individuals with ASD
  - Altered serotonin-related brain abnormalities
    - Altered firing of serotonergic neurons
    - SHT1A and SHT3A receptor hypersensitivity
Hypothesis

Genetic abnormalities in the serotonin transporter (SERT), of the kind found in autism, also cause abnormalities in gut development & function

Could the G56A mutation be a brain-gut link in ASD?

TPH1 expression is elevated but that of TPH2 is depressed in G56A mice

Total and late-born submucosal neurons are deficient in G56A (SuperSERT) mice

The G56A mutation affects the ENS independently from the CNS
Conclusions

- GI problems are frequently associated with ASD
- There are several known brain-gut links in ASD
- We evaluated ENS structure and GI function in a mouse with the common SERT-based mutation (SuperSERT) found in ASD
- ENS development, contents, susceptibility to intestinal inflammatory disease and intestinal epithelial permeability are abnormal
- GI problems are prominent in children with autism
- The serotonin transporter is the major breakdown mechanism for serotonin in the intestine
- G56A mouse model of ASD

Severity of DSS-induced colitis is significantly greater in G56A > WT mice

- Villus height, crypt depth, and proliferation in G56A mice
- DSS causes intestinal condition most similar to Ulcerative colitis in mice

Small intestinal & fecal bacteria are more abundant in G56A > WT mice. Small bowel bacterial overgrowth

So far........