“Autism-Spectrum Disorders – The Link Between Behavioral Issues and Often Overlooked Digestive System Problems”

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Lecture Overview

- What is Autism – DSM IV criteria
- Current autism statistics
- What is Autism – *Really*?
- The nightmare side of Autism
- Meet Noah
- How did I get involved with this community of patients?
- Common avoidance because of the diagnosis
- Bernard Rimland, Ph. D, and the roots of biomedical intervention for autism
- Abundance of scientific research
Common GI problems in autism
Ali, Luke, and Steven – various behaviors related to constipation
Tyler – aggression and self-injury behavior centered around eating
Inflammatory bowel disorders in autism
The case of Noah (revisited)
Can intestinal pathogens negatively influence behavior?
Lecture Overview (continued)

- Introduction to urine toxin evidence of certain clostridia bacteria and the link to autism (presentation slides of Bill Shaw, Ph.D)
- Frank – clostridia induced behavior problems?
- Suggestions for your practice
6 or more identifiers from 3 major categories:

Social interaction impairments
- Failure to use eye contact, body posture, facial expression
- Failure to develop peer relationships
- Lack of social interaction, sharing, or enjoyment with others
- Lack of social or emotional reciprocity

Communication impairments
- Delay or total lack in speech development
- Inability to initiate or maintain conversational speech
- Stereotyped or repetitive use of language

Repetitive and stereotyped behaviors, interests, and activities
- Abnormal intensity or focus on stereotyped or restricted patterns of interest
- Inflexible adherence to rituals and routines
- Repetitive movements (hand-flapping, finger flicking or twisting, or complex body movements)
- Preoccupation with parts of objects

www.cdc.gov/ncbddd/autism
For many years autism was rare - occurring in just five children out of 10,000.

Early 1990s - rate of autism diagnosis increased significantly world wide with figures as high as 60 per 10,000 children.

In March 2012, the Centers for Disease Control (CDC) stated that 1 in 88 children in the U.S. is diagnosed with an Autism-Spectrum Disorder.

2006-2008: 1 in 6 children in U.S. had developmental disability (autism, speech and language impairments, cerebral palsy, etc.)

http://www.cdc.gov/ncbddd/autism/data.html
What is Autism – Really?
Andrew – Before Autism Diagnosis
After Autism Diagnosis
Andrew Kohatsu
"Andy"
8-4-2005
"Real Smiles
Clear eyes
Happy eyes"

100%
"With us" and aware now

The pictures were taken by me, Andy’s sister Janielle.
He’s always ignored me, now he wants my attention all the time.
He tries to tickle my feet and he thinks it’s sooo funny! He’s teasing me!
>=(^_^)
Jacob
Non-communicative, fearful, anxious, and easily combative
Became happier and healthier through food allergy avoidance and gut treatment
The Faces of Autism

This is Cody. He likes roller coasters & watching videos on YouTube. His favorite television show is The Price is Right & he would live at Walt Disney World if it was possible.

He loves to give hugs & his excitement over the little things is contagious.
The Nightmare Side of Autism

help me find my smile
Self-injurious behaviour is associated with alterations in the somatosensory system in children with autism spectrum disorder

Emma G. Boccardi, Dallas Card, S. Wendy Roberts, Kathleen M. Mek-Pair, M. Malar Chakravarty, Jason P. Lerch, Mark T. Taylor

Abstract: Children with autism spectrum disorder (ASD) frequently engage in self-injurious behaviours, often in the absence of reporting pain. Previous research suggests that altered gain sensitivity and repeated exposure to noxious stimuli are associated with morphological changes in somatosensory and limbic cortices. Further evidence from postmortem studies with self-injurious adults has indicated alterations in the somatosensory and organization of the temporal lobes; however, the effect of self-injury on somatosensory development in children with ASD has not yet been determined. Thirty children and adolescents (mean age = 10.6 ± 2.5 years, range 7-15 years, 20 males) with a clinical diagnosis of ASD were measured at 17T with a 32-channel head coil. T1-weighted high-resolution images were acquired using a 3D FT spoiled gradient echo sequence. No significant group differences were observed in brain volume, surface area, or cortical thickness. Within the ASD group, self-injury scores negatively correlated with thickness in the right temporal lobe (r = 0.53, p < 0.0001), bilateral primary somatosensory cortices (SI) right hemisp: r = 0.44, p = 0.0004), and the volume of the left ventricle (V1) reduced the thickness (r = 0.52, p = 0.0008). Based on these findings, we performed an fMRI-based region-of-interest diffusion tensor imaging analysis between SI and the V1 network and found that children who engaged in self-injury had significantly lower fractional anisotropy (r = -0.24, p = 0.01) and higher mean diffusivity (r = 0.52, p = 0.003) in the ventricular system. Additionally, greater incidence of self-injury was associated with increased radial diffusivity values in bilateral posterior limits of the internal capsule. Together, these findings suggest that self-injury is related to alterations in somatosensory cortical and subcortical regions and their supporting white-matter pathways. Findings could reflect state-dependent plasticity in the somatosensory system or disrupted brain development that could serve as a risk marker for self-injury.

Keywords: Autism spectrum disorder - Injury - Grey matter - White matter - Fas
Abstract
The authors examined 183 children with autistic symptoms and found that the age-specific incidence rates of seizures in this sample were between 3 and 28 times the rates for children in the general population. The subjects classified as totally autistic were at high risk of developing seizure from early childhood well into adolescence, but especially so at puberty. The partially autistic children had an increased risk of seizures only up to age 10. The authors suggest that the high incidence of seizures at puberty observed in this study may be specific to children with total autistic symptomatology and may represent a distinct pathological process associated with autism.
Meet Noah
Sadness and Despair
Severe Head Banging
Padded Room
Exhausted From Self-Abusive Behavior
Family Trapped and On The Edge Emotionally
How Did I Get Involved With This Community Of Patients?

Started with the movie “Rain Man”
In 1998, my practice in San Diego, CA. received a flyer in the mail for an upcoming conference on autism. The conference was called DAN! (Defeat Autism Now), and was promoted to practitioners and parents interested in learning about “biomedical” (aka. biological or medical) approaches to autism. During the lectures I realized that the medical problems (immune, digestive, nutritional imbalances, etc.) that were afflicting these children were similar to many of my adult patients.
Soon after attending the DAN! Conference I started to see some autism-spectrum children in my office. I was clueless about what to do - literature on a particular company called Great Plains Laboratory, and their urine Organic Acid Test (OAT).

The OAT, is the cornerstone of Great Plains Laboratories “go to test”, and is the brainchild of founder Bill Shaw, Ph.D.

Learned from parents who were attempting various diets and supplements, i.e. gluten-free/casein-free, B-vitamins, magnesium.
A Crash Course In Integrative Medicine

Seeing some success with these interventions, not only reported by parents, but on follow-up analysis, blood testing markers, etc. I realized that there was a world of health information I needed to become familiar with.

Practice began to shift from traditional family medicine and OMT into various levels of integrative medicine - *environmental toxicity, immune dysfunction, biochemical imbalances, nutritional problems.*
I also realized that I was working with some children who were quite ill:

- Chronic bowel problems – loose stools, constipation or both
- Low thyroid
- Anemia
- Other vitamin and mineral deficiencies
- Allergies
- Frequent infections
- Immunodeficiency
- ...etc.
I also realized that the desperation amongst many parents was they were being given the cold shoulder by some in the medical profession. Their kids being essentially cast aside because of their autism diagnosis.
Child w/o Autism (example)

- Physical milestones delayed
- Chronic diarrhea – 5+ BM’s per day
- Recurrent sinus, ear & upper respiratory infections
- Eczema
- Bloating, gas and distended abdomen
- Anxiety, attention issues
- Irritable, poor sleep

Child with Autism (example)

- Physical milestones delayed
- Chronic diarrhea – 5+ BM’s per day
- Recurrent sinus, ear & upper respiratory infections
- Eczema
- Bloating, gas and distended abdomen
- Anxiety, attention issues
- Irritable, poor sleep
Dedicated to Exploring the Various Medical Complexities Seen With Autism

Defeat Autism Now!
Autism-Spectrum Disorders:

} That many individuals on the autism-spectrum are dealing with underlying medical issues that can be treated as part of their autism.

} Autism – is more than just a psychological or neurodevelopmental condition.

} Multi-system disorder that affects the brain versus just being a brain disorder.
What Are The Medical Complexities Seen In Autism?

Abundance of Research Already Exists
Neuroglial activation and neuroinflammation in the brain of patients with autism.

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Autism is a neurodevelopmental disorder characterized by impaired communication and social interaction and may be accompanied by mental retardation and epilepsy. Its cause remains unknown, despite evidence that genetic, environmental, and immunological factors may play a role in its pathogenesis. To investigate whether immune-mediated mechanisms are involved in the pathogenesis of autism, we used immunocytochemistry, cytokine protein arrays, and enzyme-linked immunosorbent assays to study brain tissues and cerebrospinal fluid (CSF) from autistic patients and determined the magnitude of neuroglial and inflammatory reactions and their cytokine expression profiles.

Brain tissues from cerebellum, midfrontal, and cingulate gyrus obtained at autopsy from 11 patients with autism (age 5 to 44 years old) were used for morphological studies. Fresh-frozen tissues available from seven patients and CSF from six living autistic patients were used for cytokine protein profiling. We demonstrate an active neuroinflammatory process in the cerebral cortex, white matter, and notably in cerebellum of autistic patients. Immunocytochemical studies showed marked activation of microglia and astroglia, and cytokine profiling indicated that macrophage chemoattractant protein (MCP)-1 and tumour growth factor-beta1, derived from neuroglia, were the most prevalent cytokines in brain tissues. CSF showed a unique proinflammatory profile of cytokines, including a marked increase in MCP-1.

Our findings indicate that innate neuro-immune reactions play a pathogenic role in an undefined proportion of autistic patients, suggesting that future therapies might involve modifying neuroglial responses in the brain.

Ann Neurol. 2005 Feb;57(2):304
Using gas chromatography/mass spectrometry, cholesterol was quantified in 100 samples from subjects with ASD obtained from the Autism Genetic Resource Exchange (AGRE) specimen repository.

Although no sample had cholesterol levels consistent with SLOS, 19 samples (19%) had total cholesterol levels lower than 100 mg/dl, which is below the 5th percentile for children over age 2 years.

NIH meta-analysis indicates less than 160mg/dl of cholesterol = 10 to 20% increased death rate. Also, low values (below 160) seem to be associated with depression, anxiety, bipolar, cancer, Parkinson’s, violent behavior and behavioral volatility.

These findings suggest that, in addition to SLOS, there may be other disorders of sterol metabolism or homeostasis associated with ASD.
Benefits of cholesterol feeding in SLOS


- Beginning to walk
- Start to run
- Growth improvement
- Less infections
- Less UV light sensitivity
- Increased alertness
- Head banging stops
- Decreased tactile defensiveness
- Increased sociability
- Behavior improves
- Talking has started in adults who were not talking before
- Verbal people say they feel better
- *Many improvements in only a few days after supplementation*
- Decreased irritability
- Increased muscle tone
Oxytocin Receptor Polymorphism and Autism

Association of the oxytocin receptor (OXTR) gene polymorphisms with autism spectrum disorder (ASD) in the Japanese population.


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Abstract

The oxytocin receptor (OXTR) gene, which is located on chromosome 3p25.3, has been implicated as a candidate gene for susceptibility of autism spectrum disorder (ASD). Positive associations between OXTR and ASD have been reported in earlier studies. However, the results were inconsistent and demand further studies. In this study, we investigated the associations between OXTR and ASD in a Japanese population by analyzing 11 single-nucleotide polymorphisms (SNPs) using both family-based association test (FBAT) and population-based case-control test. No significant signal was detected in the FBAT test. However, significant differences were observed in allelic frequencies of four SNPs, including rs2254298 between patients and controls. The risk allele of rs2254298 was 'A', which was consistent with the previous study in Chinese, and not with the observations in Caucasian. The difference in the risk allele of this SNP in previous studies might be attributable to an ethnic difference in the linkage disequilibrium structure between the Asians and Caucasians. In addition, haplotype analysis exhibits a significant association between a five-SNP haplotype and ASD.

In conclusion, our study might support that OXTR has a significant role in conferring the risk of ASD in the Japanese population.
Oxytocin Signaling and Cholesterol Dependence

Oxytocin receptors: ligand binding, signalling and cholesterol dependence.

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Abstract

The G protein coupled oxytocin receptor (OTR) reveals some specific molecular and physiological characteristics. Ligand-receptor interaction has been analysed by photoaffinity labelling, site-directed mutagenesis, the construction of receptor chimeras and molecular modelling. Major results of these studies will be summarized. The N-terminus of the OTR is mainly involved in agonist binding. Notably, antagonists that are derived from the ground structure of oxytocin, bind the receptor at distinct sites partly non-overlapping with the agonist binding site. OTRs are able to couple to different G proteins, with a subsequent stimulation of phospholipase C-beta isoforms. In dependence on G protein coupling, OTRs can transduce growth-inhibitory or proliferatory signals. Some evidence is provided that OTRs are also present in form of dimeric or oligomeric complexes at the cell surface. The affinity of the receptor for ligands is strongly dependent on the presence of divalent cations (Mg(2+)) and cholesterol that both act like positive allosteric modulators. While the high-affinity state of the receptor for agonists requires divalent cations and cholesterol, the high-affinity state for antagonists is only dependent on a sufficient amount of cholesterol. Cholesterol affects ligand-binding affinity, receptor signaling and stability. Since the purification of the OTR has never been achieved, alternative methods to study the receptor in its native environment are necessary. Promising strategies for the site-specific labelling of the OTR will be presented. The employment of diverse reporter molecules introduced at different positions within the OTR might allow us in the near future to measure conformational changes of the receptor in its native lipid environment.
Areas in red show where the brain is more active with face perception, and blue areas with non-face objects.
Ethanol, arsenic, lead, mercury, aluminum and the vaccine preservative thimerosal are suspected to be etiological factors for neurodegenerative and neurodevelopmental disorders. Autism is a neurodevelopmental disorder characterized by oxidative stress and impaired methylation status, including decreased activity of the folate and vitamin B12-dependent enzyme methionine synthase (MS). MS-mediated conversion of homocysteine to methionine is crucial for neurons and all mammalian cells to sustain normal methylation status, involving more than 100 different reactions. Glutathione (GSH) protects MS from oxidative inactivation by reactive oxygen species, while MS inactivation increases GSH synthesis by augmenting transsulfuration. Utilizing SH-SY5Y cultured human neural cells, we found that a 1 hour pre-incubation of cells with arsenic, lead, mercury, aluminum and thimerosal potently decreased both hydroxocobalamin (OHCbl) and methylcobalamin (MeCbl)-based MS activity, although OHCbl exhibited greater sensitivity than MeCbl. At a concentration of 100 nmol, each of these neurodevelopmental toxins caused a 60–70% reduction of intracellular GSH levels. 22 mM (0.1%) ethanol caused a similar inhibition of OHCbl- and MeCbl-based MS activity and a similar decrease in GSH levels.

Our findings suggest that oxidative stress may contribute to the occurrence of neurodevelopmental disorders such as autism via a mechanism that involves inhibition of Methionine Synthase activity.
Abstract
A large number of autoimmune disorders have a gastrointestinal (GI) dysfunction component that may interplay with genetic, hormonal, environmental and/or stress factors. This narrative review investigates possible links between autism, immune system abnormalities and GI symptoms in a subgroup of children with autism. A literature search on Medline (1950 to September 2010) was conducted to identify relevant articles by using the keywords 'autism and gastrointestinal' (71 publications) and 'autism and immune' (237 publications), cross-referencing and general searching to evaluate the available literature on the immunological and GI aspects of autism.

Summary: Sufficient evidence exists to support that a subgroup of children with autism may suffer from concomitant immune-related GI symptoms.
Extensive List of Published Research

www.Autism.com

100’s of published articles related to:

- Biomarkers
- Methylation
- Gastrointestinal
- Genetics
- Immune
- Metabolic
- Nutritional
- Oxidative Stress
What is Biomedical Intervention for Autism?

The attempt to improve the autistic condition by identifying physical problems (structural, biochemical, organ specific), and treating these medically. Biomedical intervention incorporates all aspects of health treatment:

- Dietary modification
- Medications
- Nutritional supplements
- Commonly used in conjunction with speech, occupational, behavior, and physical therapy.
No Magic Bullets

There is no one drug, supplement or “magic bullet” therapy for autism.
“I work with kids who have multiple medical problems including nutritional imbalances, digestive and detoxification problems, food sensitivity issues, etc.”

The common denominator is all of these kids happen to have a diagnosis of autism.
Abstract

Restricted dietary intake is common among children with behavioral issues. Here we report a case of a severely autistic child who presented initially with limp, but who soon developed cough, tachypnea, hypoxia, and tachycardia. An echocardiogram revealed evidence of pulmonary hypertension (PH) with severely dilated right ventricle and elevated right-sided pressures. The etiology of his PH was unclear but further laboratory evaluation demonstrated severe nutritional deficiencies, in particular an undetectable ascorbic acid (vitamin C) level as well as deficient levels of thiamine (vitamin B1), pyridoxine (vitamin B6), cobalamin (vitamin B12), and vitamin D. Repletion of these vitamins was associated with resolution of his PH and his musculoskeletal complaints. We report this case and a review of the relevant literature as a clinical lesson to expand the differential diagnosis of limp in children who may be difficult to assess as well as to report on an unusual association between severe vitamin deficiencies and PH.
Common GI Problems In Autism

Behavioral Issues and More
Just like everyone else, people with autism may suffer from:

- Gastritis
- GERD
- Colitis
- Irritable Bowel Syndrome
- Constipation
- Motility-based disorders
- Food allergy and sensitivity
- Overgrowth syndromes
J Dev Behav Pediatr. 2006 Apr;27 (Valicenti-McDermott M. et. al.) - evaluated children with ASD and two control groups matched for age, sex and ethnicity (one with non-autism-related developmental disorders, and the other developmentally normal). There were 50 children in each group – findings concluded:

- 70% of the children with ASD had GI Issues compared to 42% of the children with developmental disorder other than ASD.
- 28% of children with typical development.
Commonality of Food Allergies

Food allergy in this population is common - food allergy can affect any site in the GI tract. Research in the past points to the following food allergy prevalence rates in autistic children:

} 5-8% of neurotypical children without autism (Sampson, 1999) suffer food allergies.
} 36% of autistic children (Lucarelli, 1995) suffer food allergies.
Abstract:
To compare gastrointestinal (GI) problems among children with: (1) autism spectrum disorder (ASD), (2) developmental delay (DD) and (3) typical development (TD), GI symptom frequencies were obtained for 960 children from the Childhood Autism Risks from Genetics and Environment (CHARGE) study. We also examined scores on five Aberrant Behavior Checklist (ABC) subscales comparing ASD children with high versus low frequency GI symptoms. Compared to TD children, those with ASD [aOR 7.92 (4.89-12.85)] and DD [aOR 4.55 (2.51-8.24)] were more likely to have at least one frequent GI symptom. Restricting to ASD children, those with frequent abdominal pain, gaseousness, diarrhea, constipation or pain on stooling scored worse on irritability, social withdrawal, stereotypy, and hyperactivity compared with children having no frequent GI symptoms.

Summary: Frequent GI problems affect young children with ASD and DD more commonly than those with TD. Maladaptive behaviors correlate with GI problems, suggesting these comorbidities require attention.
Ali, Luke, and Steven

3 different scenarios surrounding constipation
Ali

5 years old
Age of Autism Diagnosis: 2-1/2

Main Issues:
- Expressive language (only babbles)
- Social withdrawal and avoidance
- Sound sensitivity (covers his ears)
- Non aggressive or self-injurious

Repetitive Behavior: lays flat on the floor and rubs back and forth.
PE: distended abdomen, “pregnant belly”
Ali

Parents report that he has a “normal” bowel movement everyday, but lots of foul smelling gas.

AP ABDOMEN X'RAY: (ONE VIEW):

Colonic gas and faecal residue are seen obscuring abdomen and pelvic areas.
No evidence of intestinal obstruction or perforation of viscus seen.
Luke

12 years old
Age of Autism Dx: 3 years (now considered to have Asperger’s)

Main Issues:
} Language – can have conversation
} Social – awkward. Lack of personal space boundaries
} Behaviors – easily stressed and frustrated. Chews on shirt
High anxiety – particularly at school, and associated with
bathroom use.

Concerning Behavior – becomes more obsessive and
combative emotionally when he complains of stomach
hurting.
Luke

- Luke has reported that his stomach hurts a lot after eating, and throughout the day.
- Parents notice he bends forward on toilet when having a bowel movement. Can spend upwards of 30 to 45 minutes.
- **Ped:** checked for H. pylori (negative), given reflux medications (not helpful).
- **Supplements:** magnesium oxide – seems to help stomach and bowel movements – “slightly.”
- Parents tried Ducolax suppositories when younger with some relief, but nothing consistent.
- **Referred to GI Specialist:** Rectal Prolapse – Magnesium citrate with Miralax, increase fiber, and VSL#3.
14 years old
Dx: age 2-1/2 (severe autism)
Main Issues:
  } Non-verbal
  } Poor socialization
  } Anxiety, high sensory seeking behavior, and aggression.

Main reason for consult: Aggressive behavior and destructive tantrums.
Main physical challenge: constipation – literally would not have bowel movement for 5 to 6 days.
Constipation remedies: Ducolax suppositories, Miralax – ½ cup daily (by pediatrician)
PE: Abdominal distention
Main intervention (for constipation):

- Fleet’s enema – 2 hours prior to Miralax dosing
- Miralax – ½ capful in 6 ounces of water every ½ hour for 6 dosages – then followed with a Ducolax suppository one hour later (did for 2 days in a row).
- Miralax - ½ capful twice daily for 3 weeks.
- Ground flax seeds, slippery elm herb (6 capsules daily) and Magnesium citrate 400mg daily for long-term maintenance.
Massive stool dump following 2 days of enema, Miralax and Ducolax treatment
Aggression and Tantrums Greatly Diminished

Mother reported that within 4 days of bowel evacuation his aggressive tantrums diminished 75%.

Mom reported great progress overall, i.e. happier, more calm, less agitated, better sleep, but still remained aggressive at times – particularly when he was being reprimanded for negative behavior.

I inquired further about his aggressive behavior patterns.
Not Everything Is A “Biomedical” Issue With These Kids

Steven only hit mom, sister, aunt, and in the past grandma.

Didn’t hit his brother, father or grandfather.

Grandma got tired of being hit, and one day she slapped him in the face and stated “don’t ever hit me again.”

He never hit his grandmother again.
Tyler

Aggression and Self-Injurious Behavior – Often Associated With Eating
Tyler

- 7 years old
- Twin - born via C-section
- Age of Autism Dx: 2 y/o
- Autism Issues – lack of expressive language development, poor social interaction and interest, stimulatory behavior – finger flicking, finger/hand twisting.
- Prior Medical Issues – projective vomiting episodes around 1 year of age, suspected reflux.
- Feeding Issues – generally a fussy and picky eater
- Significant Behavior Issues – began Spring of 2013 – self-injurious (head-banging, biting hands) and aggression (particularly around meal time).
Aggression occurred shortly after moving from Texas to Kentucky.

Started to have allergies symptoms, i.e. itchy eyes, runny nose, sneezing – placed on Zyrtec.

Some relief with allergies, but continued with aggressive behavior associated with meals.

Referral to pediatric GI specialist who performed endoscopy.

Dx: Eosinophilic Esophagitis
Component Results

PATHOLOGY/GENETICS RESULTS:

SURGICAL PATHOLOGY REPORT

Specimen(s) Received
A: Esophagus, biopsy-mid level
B: Esophagus, biopsy-distal
C: Stomach, biopsy
D: Duodenum, biopsy

Diagnosis

A - ESOPHAGUS, BIOPSY:
   - INTRAPITHELIAL EOSINOPHILIA (MAXIMUM COUNT 3/HPF)

B - ESOPHAGUS, DISTAL, BIOPSY:
   - INTRAPITHELIAL EOSINOPHILIA (MAXIMUM COUNT 45/HPF)
   - MILD CHRONIC MUCOSAL CHANGES

C - STOMACH, BIOPSY:
   - MILD SUPERFICIAL CHRONIC GASTRITIS (SEE MICROSCOPIC DESCRIPTION)

D - DUODENUM, BIOPSY:
   - NO SPECIFIC PATHOLOGIC DIAGNOSIS
   - FOCALLY PROMINENT EOSINOPHILS IN LAMINA PROPRIA
Tyler – Eosinophilic Esophagitis

Microscopic Description

A - Sections of esophageal squamous mucosa show a scanty intraepithelial eosinophilic infiltrate, ranging in density up to 3/HPF in areas of most severe involvement. No significant chronic mucosal changes are present.

B - Sections show esophageal squamous mucosa with underlying submucosal fibroconnective tissue. There is a diffuse intraepithelial eosinophilic infiltrate ranging in density up to 45/HPF in areas of most severe involvement. Mild basal cell hyperplasia is evident.

C - Sections of gastric mucosa show patchy expansion of the superficial lamina propria by chronic inflammatory cells (plasma cell predominant), within the antral biopsy pieces. Scattered eosinophils are also present within the lamina propria. No active inflammation is identified. Immunohistochemical stain for H. pylori microorganisms is negative.

D - Sections of duodenal mucosa show well preserved villous and crypt architecture, an intact enterocyte population and brush border with no evidence of active inflammation. Focally prominent clusters of eosinophils are present in the lamina propria.

Placed on Zantac 75mg BID, plus restricted diet
Reported behavior improvements from parents: within 2 weeks of initial therapy his self-injurious and aggressive behavior diminished by 75 to 80%, and within 1 month there were no more issues. Tyler for the first time had typical eating behaviors.
Digging Deeper
Inflammatory Bowel Problems Often Go Undiagnosed
“Gastrointestinal Pathology in Autism: Description and Treatment”
by Arthur Krigsman, M.D.

Normal Tissue

Eosinophil infiltration of esophagus – can be triggered by reflux disease which is common in ASD.
Ulcers and Polyps

Duodenal Ulcer

Inflammatory Stomach Polyp
Dr. Krigsman describes finding bile refluxing into the esophagus.
Breathed smelled like feces.
Caused by slow intestinal motility.
H. pylori and even Candida infections are found.
Food avoidance, pounding on chest, holding stomach in association with tantrums, aggression, etc. Could it be caused by pain?
Poor intestinal motility can lead to severe reflux.

Some ASD kids have motility problems leading to distended abdomens.

**Distention Types Seen in ASD:**

- **Lower (pregnant)** – intestines and colon are full of gas and stool
- **Upper (just below rib cage)** – food is stuck in stomach
Inflammation can be non-specific, but it does indicated white blood cell infiltration into mucosal tissue.

**Inflammation Can:**
- Cause pain
- Destroy cellular tissue
- Suppress enzyme function
- Blunt absorption
- Suppress SIgA production
- Effect GI motility
- ...and more!

Lymphonodular Hyperplasia of the Duodenum
The Ileum is the last part of the small intestine.

High immunologically reactive area - large amount of lymphoid tissue.

An area that is commonly affected in ASD.

**Signs and Symptoms:**

- Diarrhea or constipation
- Self-injurious behavior (SIB)
- Food avoidance
- Poor sleep
- Poor absorption and growth
Large Bowel Inflammation

Inflammatoty Polyp

Ulcerations in Large Bowel
Occasional loose stools are normal part of our existence. However, as Dr. Krigsman explains in his article, “if most or all of the stools are unformed – it is pathologic.”
Posturing across the edge of a table, the arm of a chair or couch, or pressing abdomen into the floor is not normal. It may be a sign of intestinal pain.
Is self-injurious behavior a normal part of autism? In many children it is triggered because of pain. This behavior warrants investigation and any sign of intestinal issues need to be assessed for underlying pathology.
Noah
Revisited
Noah’s History

- Non-complicated delivery
- Hit physical milestones normally
- Colicky as a baby, and few ear infections
- Tendency towards constipation by age one year.
- Expressive language delay, but receptive language seemed typical.
- By 1-1/2 years lacked typical social bonding and preferred to alone.
- By 2 years expressive language was not progressing. Showing signs of anxiety.
- Suspected ASD around age 2-1/2 years
- Began to develop more ear and respiratory infections with repeat antibiotics.
- By age 4 bowels began to alternate between loose and constipation. Started to become more rigid in his behavior, anxious.
Age 5 – increased anxiety. Treated with Ativan and Risperdal. Developed suspected TD from Risperdal.

Age 5-1/2 – Dx: Absence Seizures. Treated with Trileptal which did help some with expressive language.

Age 6 – After treatment course of antibiotics for strep infection Noah began to manifest with heightened anxiety and new obsessive compulsive behavior, as well as guttural throat sounds.


Age 7 – blood testing revealed low immunoglobulins, but high ASO titer – suspected PANDAS.
Noah’s History

- Multiple treatment courses of Zithromax helped throat sounds and repetitive behavior (approx. 70 to 75%). Appeared more calm overall when on antibiotics.
- Given IVIG therapy for 6 months – further improvement in OCD behavior. No longer with throat noises.
- From age 8 to 12 he was back and forth with Zithromax prescriptions, anti-anxiety medications, i.e. Ativan, and behavioral and speech therapy.
- Overall, was improved, and did not exhibit aggressive or self-injurious behavior, but still autistic.
March 2012 – developed “stomach virus” – 4 days of nausea, vomiting, high fever. Was lethargic and in bed most of the time.

On day 5 – got up from bed and ran into wall. Began to head-bang and have violent aggression.

Shortly thereafter he started with abdominal posturing over furniture, and worsening stool pattern (loose).

In fact, all along mother reports that digestion “never appeared normal.”
Admitted to ER within a few weeks and kept in sedation.
Laboratory testing apparently revealed no source of acute infection, and he was eventually discharged for outpatient follow-up with Psychiatrist.
Was placed back on Risperdal by Psychiatrist which did help to calm him down. However, volatility and anxiety still an issue at times. Continued to have loose bowels and furniture posturing.
Started working with integrative medicine physician in Los Angeles who diagnosed a wide variety of environmental and food allergies. Still had persistent bowel problems.
Referred back to primary care physician for GI referral. GI refused scope procedure after physical examination.
My consultation begins with a referral to GI specialist Dr. Krigsman. Krigsman scopes and finds Noah to have abundant inflammatory lesions throughout bowel. Treatment approach similar to Chron’s disease, i.e. Entecort, Pentasa.
Noah Today

- Violent outbursts almost non-existent
- Still with anxiety, but manageable
- Digestion – having formed stools for first time in years.
- Still needs behavioral intervention, but severity of prior behavioral problems significantly reduced.
- Family currently in fight with insurance company for ongoing medical treatment.
- Situation appears stable – for the moment.
GI Pathogens
Can They Negatively Influence Behavior?
11 children with regressive-onset autism were recruited for an intervention trial using a minimally absorbed oral antibiotic. Entry criteria included antecedent broad-spectrum antimicrobial exposure followed by chronic persistent diarrhea, deterioration of previously acquired skills, and then autistic features. Short-term improvement was noted using multiple pre- and post-therapy evaluations. These included coded, paired videotapes scored by a clinical psychologist blinded to treatment status; these noted improvement in 8 of 10 children studied. Unfortunately, these gains had largely waned at follow-up.

“Although the protocol used is not suggested as useful therapy, these results indicate that a possible gut flora-brain connection warrants further investigation, as it might lead to greater pathophysiologic insight and meaningful prevention or treatment in a subset of children with autism.”
Demonstrate GI barrier defects and microbiota alterations in the maternal immune activation (MIA) mouse model that is known to display features of ASD.

Oral treatment of MIA offspring with the human commensal *Bacteroides fragilis* corrects gut permeability, alters microbial composition, and ameliorates defects in communicative, stereotypic, anxiety-like and sensorimotor behaviors. MIA offspring display an altered serum metabolomic profile (4-ethylphenylsulphate), and *B. fragilis* modulates levels of several metabolites.

Treating naive mice with a metabolite that is increased by MIA and restored by *B. fragilis* causes certain behavioral abnormalities, suggesting that gut bacterial effects on the host metabolome impact behavior.

“Taken together, these findings support a gut-microbiome-brain connection in a mouse model of ASD and identify a potential probiotic therapy for GI and particular behavioral symptoms in human neurodevelopmental disorders.”
The effects of Clostridial bacteria metabolism on gastrointestinal function and mental health and neurotransmitter balance

William Shaw Ph.D.
The Great Plains Laboratory
www/GPL4U.com
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The Great Plains Laboratory is fully certified under the federally mandated Clinical Laboratory Improvement Amendments (CLIA). All referral laboratories used by The Great Plains Laboratory are also CLIA certified. The CLIA license means the laboratory has met a number of federal standards for operating a laboratory.

Proficiency Testing

The Great Plains Laboratory voluntarily participates in all proficiency programs offered by the College of American Pathologists (CAP).
William Shaw, Ph.D., is board certified in the fields of clinical chemistry and toxicology by the American Board of Clinical Chemistry. Before he founded The Great Plains Laboratory, Inc., Dr. Shaw worked for the Centers for Disease Control and Prevention (CDC), Children's Mercy Hospital, University of Missouri at Kansas City School of Medicine, and Smith Kline Laboratories. He is the author of Biological Treatments for Autism and PDD, originally published in 1998 and Autism: Beyond the Basics, published in 2009. He is also a frequent speaker at conferences worldwide.

Dr. Shaw is the stepfather of a child with autism and has helped thousands of patients and medical practitioners to successfully improve the lives of people with autism, AD(H)D, Alzheimer's disease, arthritis, bipolar disorder, chronic fatigue, depression, fibromyalgia, immune deficiencies, multiple sclerosis, OCD, Parkinson's disease, seizure disorders, tic disorders, Tourette syndrome, and other serious conditions.
People may advise you to listen to your gut instincts: now research suggests that your gut may have more impact on your thoughts than you ever realized. Scientists from the Karolinska Institute in Sweden and the Genome Institute of Singapore led by Sven Pettersson recently reported in the Proceedings of the National Academy of Sciences that normal gut flora, the bacteria
Mind-altering microorganisms: the impact of the gut microbiota on brain and behaviour

John F. Cryan\textsuperscript{1,2} and Timothy G. Dinan\textsuperscript{1,3}

Abstract | Recent years have witnessed the rise of the gut microbiota as a major topic of research interest in biology. Studies are revealing how variations and changes in the composition of the gut microbiota influence normal physiology and contribute to diseases ranging from inflammation to obesity. Accumulating data now indicate that the gut microbiota also communicates with the CNS — possibly through neural, endocrine and immune pathways — and thereby influences brain function and behaviour. Studies in germ-free animals and in animals exposed to pathogenic bacterial infections, probiotic bacteria or antibiotic drugs suggest a role for the gut microbiota in the regulation of anxiety, mood, cognition and pain. Thus, the emerging concept of a microbiota–gut–brain axis suggests that modulation of the gut microbiota may be a tractable strategy for developing novel therapeutics for complex CNS disorders.
Ingestion of *Lactobacillus* strain regulates emotional behavior and central GABA receptor expression in a mouse via the vagus nerve

Javier A. Bravo\(^{a,1}\), Paul Forsythe\(^{b,c,1}\), Marianne V. Chew\(^b\), Emily Escaravage\(^b\), Hélène M. Savignac\(^{a,d}\), Timothy G. Dinan\(^{a,e}\), John Bienenstock\(^{b,f,2}\), and John F. Cryan\(^{a,d,g,2}\)

\(^a\)Laboratory of NeuroGastroenterology, Alimentary Pharmabiotic Centre, \(^b\)School of Pharmacy, and Departments of \(^c\)Psychiatry and \(^d\)Anatomy, University College Cork, Cork, Ireland; \(^e\)The McMaster Brain–Body Institute, St. Joseph's Healthcare, Hamilton, ON, Canada L8N 4A6; and Departments of \(^f\)Medicine and \(^g\)Pathology and Molecular Medicine, McMaster University, Hamilton, ON, Canada L8S 4L8

Edited by Todd R. Klaenhammer, North Carolina State University, Raleigh, NC, and approved July 27, 2011 (received for review February 27, 2011)

There is increasing, but largely indirect, evidence pointing to an effect of commensal gut microbiota on the central nervous system (CNS). However, it is unknown whether lactic acid bacteria such as *Lactobacillus rhamnosus* could have a direct effect on neurotransmitter receptors in the CNS in normal, healthy animals. GABA is the main CNS inhibitory neurotransmitter and is significantly involved in regulating many physiological and psychological processes. Alterations in GABAergic system have important roles in the development of stress-related psychiatric conditions.

Probiotic bacteria are living organisms that can inhabit the gut and contribute to the health of the host (14). Accumulating clinical evidence suggests that probiotics can modulate the stress response and immune function and exhibit potential in patients with chronic...
THE OCCURRENCE OF (−)-β-m-HYDROXYPHENYLHYDRACRYLIC ACID IN HUMAN URINE*

BY MARVIN D. ARMSTRONG AND KENNETH N. F. SHAW
(From the Laboratory for the Study of Hereditary and Metabolic Disorders, and the Departments of Biological Chemistry and Medicine, University of Utah College of Medicine, Salt Lake City, Utah)

(Received for publication, June 26, 1956)
Journal of Biological Chemistry 225:269-278, 1957

“It was observed that mentally ill patients, in general, seem to excrete much larger amounts of HPHPA than do most normal people.”

“Most patients with mental retardation excrete very low amounts of HPHPA.”
Increased urinary excretion of a 3-(3-hydroxyphenyl)-3-hydroxypropionic acid (HPHPA), an abnormal phenylalanine metabolite of Clostridia spp. in the gastrointestinal tract, in urine samples from patients with autism and schizophrenia

William Shaw

The Great Plains Laboratory, Inc., Lenexa, Kansas, USA

A compound identified as 3-(3-hydroxyphenyl)-3-hydroxypropionic acid (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 source of this compound appears to be multiple species of anaerobic bacteria of the Clostridium genus. 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 (stereotypical behavior, hyperactivity, and hyper-reactivity) in experimental animals.
Structure of 3- (3- hydroxyphenyl)-3- hydroxypropionic acid

Hydroxyl group

Phenyl group

Propionic acid
Endoscopy of colon of patient with severe Clostridium difficile overgrowth-pseudomembranous colitis
Clostridia by electron microscopy
Clostridia species that produce HPHPA precursors
Shaw, Nutritional Neuroscience 2010 Vol 13 No 3: 1–10

- C. difficile-
  pseudomenbranous colitis
- C. sporogenes
- C. botulinum- food poisoning

- C. mangenotii
- C. ghoni
- C. bifermentans
- C. caloritolerans
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<td>C. lentoputrescens</td>
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<tr>
<td>C. tetanomorphum</td>
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Status of approximately 80 other species of Clostridia in GI tract unknown.
Areas of brain producing dopamine
Critical effect of intestinal bacteria on brain neurotransmitters
Effect of HPHPA on neurotransmitters—severe autism—case 1

- HPHPA mmol/mol creatinine
- HVA, VMA mmol/mol creatinine
- Time (calendar date)

Graph showing the effect of HPHPA on neurotransmitters such as HVA (dopamine) and VMA (norepinephrine) over time from 6/1/2008 to 6/2013.
Effect of HPHPA on neurotransmitters—severe autism—case 2

HPHPA mmol/mol creatinine

HVA (dopamine)

HVA (dopamine)

VMA (norepinephrine)

HPHPA Clostridia

VMA, VMA mmol/mol creatinine

Time (calendar date)
Values for HPHPA Clostridia metabolite in urine samples of male infants, control boys, and boys with autism.

W Shaw Nutr Neuroscience 2010 Vol 13 No 3: 1-10
Dopamine is a very reactive molecule compared with other neurotransmitters, and dopamine degradation naturally produces oxidative species.

More than 90% of dopamine in dopamine neurons is stored in abundant terminal vesicles and is protected from degradation.

However, a small fraction of dopamine is cytosolic, and it is the major source of dopamine metabolism and presumed toxicity.
Cytosolic dopamine undergoes degradation to HVA, as well as extremely toxic dopamine metabolites and oxidative species which deplete brain glutathione.

These toxic metabolites caused by excess dopamine may cause severe neurodegeneration of neural pathways that utilize dopamine as a neurotransmitter.
Overstimulation of dopamine tracts

Substitution of dopamine into norepinephrine tracts and sympathetic nervous system.

Damage to neurons producing excess dopamine due to oxidative damage of abnormal dopamine metabolites.

Depletion of glutathione in brain making it susceptible to other toxic chemicals.
Properties of Clostridia bacteria

- Strict anaerobe - dies when exposed to oxygen
- Causes tetanus, diarrhea, and botulism (food poisoning).
- Forms spores that are highly resistant to heat and antibiotics.
- About 100 species of Clostridia in GI tract
- Controlled by vancomycin, metronidazole, and Lactobacillus acidophilus GG.
Recurrences occur in after use of metronidazole and/or vancomycin.

Spores not killed by common disinfectants like alcohol hand wipes may actually help spores spread.

Only bleach kills spores.

Carriers without symptoms may spread spores.
Effect of metronidazole on urine HPHPA levels in autism
William Shaw Nutritional Neuroscience 2010 Vol 13 No 3: 1–10

Start metronidazole

Days after start of treatment

Stop metronidazole
## Organic acid test—urine

### Bacterial

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<th>Upper Limit</th>
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### Neurotransmitters

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<tr>
<td>HVA</td>
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<td>7.5</td>
<td>35.07</td>
<td>H</td>
</tr>
<tr>
<td>VMA</td>
<td>1.0</td>
<td>4.7</td>
<td>7.17</td>
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</tr>
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</table>
Clinical usefulness of Clostridia treatments

- Schizophrenia
- Psychosis
- Depression
- Chronic fatigue
- Tics, Tourette’s
- Autism
- Parkinson’s disease
- ADD, ADHD
- Obsessive compulsive disorder
- Seizure disorders
- Gastrointestinal disorders, diarrhea, constipation, irritable bowel, Crohn’s disease
Factors involved in autism, Clostridia toxicity measured in urine organic acid test

} **HVA**- *(homovanillic acid)*- Major metabolite of dopamine, a major brain neurotransmitter associated with abnormal autistic behavior when it is elevated.

} **VMA**- *(vanillylmandelic acid)*- Major metabolite of norepinephrine and epinephrine- important for the exploratory behavior essential for learning relations between sensory input, decision processing, motor output, and behavioral feedback.
Demonstrate GI barrier defects and microbiota alterations in the maternal immune activation (MIA) mouse model that is known to display features of ASD. Oral treatment of MIA offspring with the human commensal *Bacteroides fragilis* corrects gut permeability, alters microbial composition, and ameliorates defects in communicative, stereotypic, anxiety-like, and sensorimotor behaviors. MIA offspring display an altered serum metabolomic profile: 4-ethylphenylsulphate. Treating naive mice with a metabolite that is increased by MIA and restored by *B. fragilis* causes certain behavioral abnormalities, suggesting that gut bacterial effects on the host metabolome impact behavior.

“Taken together, these findings support a gut-microbiome-brain connection in a mouse model of ASD and identify a potential probiotic therapy for GI and particular behavioral symptoms in human neurodevelopmental disorders.”
4-ethylphenylsulphate

The researchers further dissected what was going on by screening for chemicals in the blood that differed between autistic and wild-type mice. One compound, 4-ethylphenylsulphate (4EPS), stood out:

1. It was found at levels 46 times higher in autistic mice.
2. Injecting 4EPS into wild-type mice resulted in autism-like behaviors. It’s still unclear if *B. fragilis* is producing 4EPS, however.

4EPS – Is similar in chemical structure to 4-Cresol which is known to inhibit Dopamine Beta-Hydroxylase.
Frank

Clostridia induced behavior problems?
Age: 5 y/o (time of first visit)
Diagnosis: Autism

Developmental History:

- C-section (planned), no pregnancy complications
- Colic as infant
- Typical development up to approximately 10 months, but parents did report he seemed to lack a lot of need for physical contact.
- Breastfed for one year, then began cow dairy and solids around 6 months.
Developmental History (continued):

- Eye contact okay up to 10-11 months which then started to disappear.
- Was playful and happy overall. Engaging with sibling.
- Physical milestones appeared fine.
- Was babbling, but never any word development – which never came.
- Around 15 months parents notified pediatrician of their concerns regarding language.
- Encouraged to wait a little longer to see how things progressed.
Medical History:

- Multiple ear infections during first 2 years – parents report “it always seemed like he was on antibiotics for ear problems.”
- **Digestion** – hard stools even in first year and second year. Parents needed to use periodic suppositories.
- Around 18 months developed intestinal infection – fever and diarrhea for 3 days – given multiple dosages of Tylenol to suppress fever. No antibiotics were given – felt to be viral.
Frank

Medical History (continued):

- Within 2 weeks after onset of fever and diarrhea “he seemed more agitated and irritable. Also, “didn’t have normal appetite.”
- By 20 months “seemed to disappear.”
- No expressive language, poor social interaction, not interested in sibling or neighbor kids anymore.
- Became easily agitated, side-glancing while standing close to TV screen.
- Hand-flapping, finger twisting became his fixation.
Frank

**Pediatrician** – referred to neurologist for evaluation

**Neurologist** – performed Fragile X test (normal). Stated nothing else he could do. Dx: Autism

**Biomedical Intervention (through parents own research):**

- Casein-free diet – improved eye contact, began to sleep through the night (occurred within 2 weeks)
- Gluten-free diet – no noticeable changes observed.
- Probiotic – better stools, better mood.
- Started multivitamin/mineral – made him hyper and agitated – *parents stopped after 3 weeks.*

*Overall, for the next year things seemed to stabilize regarding his autism and physical health.*
Frank

Biomedical Intervention:

- At age 4 years developed upper respiratory infection – given antibiotic treatment.
- Within the week of completing the treatment he became unusually agitated and aggressive – hitting, screaming, scratching, and biting. Was not consolable.
- Behavior “off and on” for 2 weeks, but never fully went away.
- Parents implemented Grapefruit Seed Extract and Caprylic Acid which helped with eye contact and lessoned aggressive behavior.
My Suspicion: digestive bacterial problem contributing to behavioral issues.

Organic Acid Test (from GPL):
- HPHPA – greater than 700
- HVA – 15 (indicating inhibition of Dopamine-Beta Hydroxylase from HPHPA)
Treatment:

- **Flagyl** - 40mg/kg split dose TID for 10 days.
- **Nystatin** – 500,000 units TID for 30 days
- **Culturelle (acidophilus GG)** – 3 capsules daily for 2 weeks following the Flagyl, then 2 capsules daily for maintenance.
Frank

Follow-up:

- 5 days into Flagyl treatment aggression and irritability disappeared completely.
- Within 3 weeks he was happy, content, and playful.
- Parents continue with GFCF diet and probiotics
- Overall, gains in cognitive development and behavior seen for the ensuing months.
- Requested repeat OAT to confirm
- Lost to follow-up
What You Can Do To Help More Individuals With Autism

• Be open to evaluating them medically
• Start doing some comprehensive blood testing to look for nutritional deficiencies, thyroid imbalances, and lipid profiles.
• Be willing to work with parents – many times all that a parent wants is a doctor who will try their best to help them.
What You Can Do To Help More Individuals With Autism

} Don’t be fooled by the autism label
} Start learning how to use the Organic Acid Test (OAT) in your practice for patients.
} Attend some physician trainings on Integrative Medicine as a way to expand your skills in clinical practice.
} Don’t be bashful about asking for help
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