

Journal articles regarding autism and gastrointestinal abnormalities

The attached citation from Jyonouchi is an incredibly important new piece of scientific evidence. For the first time, we have scientific validation for the dietary interventions so many parents have found useful. Most important, this validation is based not on an opioid excess theory, but on an immune model. For all of you who have run into resistance from doctors, spouses, schools and relatives, this is the first bit of concrete evidence you can show them that demonstrates a rigorous basis for elimination diets in autism.

I have read through it and would offer the following five summary points.

1. The authors demonstrate conclusively that there is an abnormal immune response to cow's milk protein (CMP), wheat protein (gliadin) and soy in ASD children. This is compared to a control group. The abnormal response is similar, though not identical, to the response of a group of children with "dietary protein intolerance" (DPI). Siblings of the ASD kids showed sensitivity to milk (CMP) but not to gliadin or soy. The ASD results were strongest for milk, followed by gliadin and then soy. All were statistically significant.
2. The authors tested the immune response by exposing white blood cells (more specifically, peripheral blood mononuclear cells, or PBMCs) to these proteins and observing the resulting production of three cytokines: TNF-alpha, IFN-gamma and IL-5. TNF-alpha production was the highest, followed by IFN-gamma. IL-5 production did not increase. Interestingly, this is a Th-1 response to these food proteins, NOT consistent with a Th2 shift as we so often hear. The authors suggest that the higher level of TNF-alpha is consistent with a Th1 response characterized by T cell activation of monocytes and macrophages that in turn also produce TNF-a.
3. The specific protein sensitivity in milk (CMP) was highest in beta-lactoglobulin and also significant in casein and alpha-lactoalbumin, though less so. This suggests that milk proteins in general are the issue, not just casein. So the "casein-free" label is a bit misleading. The real issue is milk protein more broadly.
4. Virtually all of the ASD subjects (61 of 63) who tried an elimination diet (63 of 72 tried a gf/cf/sf diet) reported improvements in GI symptoms and some autistic behaviors. 54 of these 61 had cytokine response more than two standard deviations above the control averages. This was not a blinded assessment, obviously, but provides strong scientific support for what many of us have seen from elimination diets. What is interesting is that the diet model is NOT THE SAME as the opioid model, but is based on a variable immune response in which: not every child will show sensitivity to every food; milk elimination will be the most useful step; and soy may be more important than wheat in some kids. This is very consistent with what parents report.
5. One of the more intriguing findings is the possible connection to the gut flora. The authors suggest that the root cause of the food protein sensitivity may be an underlying sensitivity to endotoxin (or lipopolysaccharides, aka LPS). LPS comes from surfaces of gram-negative bacteria in the gut flora (bordetella pertussis is also a gram-negative bacteria). In the ASD kids, but less so in the DPI kids, the cytokine responses to milk and wheat were highly

correlated with the cytokine response to LPS. This suggests that the ASD immune responses to LPS "predispose these children to sensitization to dietary proteins." This is consistent with a model of abnormal gut flora development that promotes immune response to gut bacteria: i.e., ASD kids may develop a kind of auto-immune response to their own gut flora! This, in turn, may be helped along by the early mercury and anti-biotic exposures. (Mark Blaxill)

Neuropsychobiology 2002;46(2):76-84

Innate Immunity Associated with Inflammatory Responses and Cytokine Production against Common Dietary Proteins in Patients with Autism Spectrum Disorder.

Jyonouchi H, Sun S, Itokazu N. Department of Pediatrics, University of Minnesota, Minneapolis, Minn., USA

Objectives: Children with autism spectrum disorder (ASD) frequently reveal various gastrointestinal (GI) symptoms that may resolve with an elimination diet along with apparent improvement of some of the behavioral symptoms. Evidence suggests that ASD may be accompanied by aberrant (inflammatory) innate immune responses. This may predispose ASD children to sensitization to common dietary proteins (DP), leading to GI inflammation and aggravation of some behavioral symptoms.

Methods: We measured IFN-gamma, IL-5, and TNF-alpha production against representative DPs [gliadin, cow's milk protein (CMP), and soy] by peripheral blood mononuclear cells (PBMCs) from ASD and control children [those with DP intolerance (DPI), ASD siblings, and healthy unrelated children]. We evaluated the results in association with proinflammatory and counter-regulatory cytokine production with endotoxin (LPS), a microbial product of intestinal flora and a surrogate stimulant for innate immune responses. **Results:** ASD PBMCs produced elevated IFN-gamma and TNF-alpha, but not IL-5 with common DPs at high frequency as observed in DPI PBMCs. ASD PBMCs revealed increased proinflammatory cytokine responses with LPS at high frequency with positive correlation between proinflammatory cytokine production with LPS and IFN-gamma and TNF-alpha production against DPs. Such correlation was less evident in DPI PBMCs.

Conclusion: Immune reactivity to DPs may be associated with apparent DPI and GI inflammation in ASD children that may be partly associated with aberrant innate immune response against endotoxin, a product of the gut bacteria. Copyright 2002 S. Karger AG, Basel PMID: 12378124 [PubMed - in process]

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Original Article

Evaluation of an association between gastrointestinal symptoms and cytokine production against common dietary proteins in children with autism spectrum disorders

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Objective

To evaluate an association between cytokine production with common dietary proteins as a marker of non-allergic food hypersensitivity (NFH) and gastrointestinal (GI) symptoms in young children with autism spectrum disorders (ASD).

Study design

Peripheral blood mononuclear cells (PBMCs) were obtained from 109 ASD children with or without GI symptoms (GI [+] ASD, N = 75 and GI [-] ASD, N = 34), from children with NFH (N = 15), and control subjects (N = 19). Diarrhea and constipation were the major GI symptoms. We measured production of type 1 T-helper cells (Th1), type 2 T-helper cells (Th2), and regulatory cytokines by PBMCs stimulated with whole cow's milk protein (CMP), its major components (casein, β -lactoglobulin, and α -lactalbumin), gliadin, and soy.

Results

PBMCs obtained from GI (+) ASD children produced more tumor necrosis factor- α (TNF- α)/interleukin-12 (IL-12) than those obtained from control subjects with CMP, β -lactoglobulin, and α -lactalbumin, irrespective of objective GI symptoms. They also produced more TNF- α with gliadin, which was more frequently observed in the group with loose stools. PBMCs obtained

from GI (-) ASD children produced more TNF- α /IL-12 with CMP than those from control subjects, but not with β -lactoglobulin, α -lactalbumin, or gliadin. Cytokine production with casein and soy were unremarkable.

Conclusion

A high prevalence of elevated TNF- α /IL-12 production by GI (+) ASD PBMCs with CMP and its major components indicates a role of NFH in GI symptoms observed in children with ASD.

Abbreviations: ASD, Autism spectrum disorders; CMP, Cow's milk protein; CM, Control mean; DP, Dietary protein; GI, Gastrointestinal; GI (+) ASD children, Children with ASD who have positive GI symptoms; IFN- γ , Interferon- γ ; IL, Interleukin; NFH, Non-allergic food hypersensitivity; PBMC, Peripheral blood mononuclear cell; PDD-NOS, Pervasive developmental disorder not otherwise specified; Th1 and Th2 cells, Type 1 and type 2 T-helper cells; TNF- α , Tumor necrosis factor- α

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Innate Immunity Associated with Inflammatory Responses and Cytokine Production against Common Dietary Proteins in Patients with Autism Spectrum Disorder

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Neuropsychobiology 2002;46:76-84 (DOI: 10.1159/000065416)

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Panenteric IBD-like disease in a patient with regressive autism shown for the first time by the wireless capsule enteroscopy: another piece in the jigsaw of this gut-brain syndrome? *Am J Gastroenterol.* 2005 Apr;100(4):979-81.

Balzola F, Barbon V, Repici A, Rizzetto M, Clauser D, Gandione M, Sapino A.

[No Abstract Available.]

Gastrointestinal complaints and diagnosis in children: a population-based study. Acta Paediatr. 2004 Jul;93(7):880-6.

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AIM: To find out the extent to which children at 10-11 y of age suffer from various gastrointestinal complaints and how often a food-induced or other diagnostic disorder might be assessed behind them, we carried out a population-based survey of 404 children in a rural Finnish town. **METHODS:** A questionnaire filled in retrospectively by their parents was used to describe the frequency of various abdominal symptoms during the previous 2 y and to select the symptomatic subjects for closer clinical examination. In the clinical investigation of the children, an elimination challenge with milk protein and lactose intolerance tests, as well as endoscopic examinations in selected cases and blood tests, were performed. **RESULTS:** In all, 110 (27%) subjects reported some gastrointestinal (GI) complaints during the last 2 y; 64 (16%) meeting the Apley criteria for recurrent abdominal pain. A specific organic or functional disorder was found in 26 subjects (6%), two having no GI symptoms. Milk protein intolerance was the most common specific disorder diagnosed in nine subjects (2.2%), followed by lactose intolerance in eight (2%), coeliac disease in five (1.2%) and *Helicobacter pylori* infection in three (0.7%). An endoscopic examination performed on 17 subjects (4.2%) and a colonoscopy on three revealed significant findings in 11; lymphonodular changes being most common, occurring in five subjects. Subjects with milk protein-induced disorders showed significantly lower IgA-class antibodies to milk and its fractions than the non-symptomatic controls. Chronic diseases, short breastfeeding, GI problems and food intolerance during the first year of life were observed as significant risk factors in determining whether a subject belonged to the group experiencing any GI complaints. **CONCLUSION:** We conclude that in one in five of those with any, even mild, GI complaints we were able to assess a specific organic disease; milk-induced disorders being most common. A milk protein and/or lactose load test, completed in some cases with an endoscopic examination, would help in assessing a proper individual diagnosis.

Focal-enhanced gastritis in regressive autism with features distinct from Crohn's and *Helicobacter pylori* gastritis.

Am J Gastroenterol. 2004 Apr;99(4):598-605.

Torrente F, Anthony A, Heuschkel RB, Thomson MA, Ashwood P, Murch SH.

The Centre for Paediatric Gastroenterology, Department of Histopathology, Royal Free & University College Medical School, London.

BACKGROUND: Immunohistochemistry allowed recent recognition of a distinct focal gastritis in Crohn's disease. Following reports of lymphocytic colitis and small bowel enteropathy in children with regressive autism, we aimed to see whether similar changes were seen in the stomach. We thus studied gastric antral biopsies in 25 affected children, in comparison to 10 with Crohn's disease, 10 with *Helicobacter pylori* infection, and 10 histologically normal controls. All autistic, Crohn's, and normal patients were *H. pylori* negative. **METHODS:** Snap-frozen antral biopsies were stained for CD3, CD4, CD8, gamma delta T cells, HLA-DR, IgG, heparan sulphate proteoglycan, IgM, IgA, and C1q. Cell proliferation was assessed with Ki67. **RESULTS:** Distinct patterns of gastritis were seen in the disease states: diffuse, predominantly CD4+ infiltration in *H. pylori*, and focal-enhanced gastritis in Crohn's disease and autism, the latter distinguished by striking dominance of CD8+ cells, together with increased intraepithelial lymphocytes in surface, foveolar and glandular epithelium. Proliferation of foveolar epithelium was similarly increased in autism, Crohn's disease and *H. pylori* compared to controls. A striking finding, seen only in 20/25 autistic children, was colocalized deposition of IgG and C1q on the subepithelial basement membrane and the surface epithelium. **CONCLUSIONS:** These findings demonstrate a focal CD8-dominated gastritis in autistic children, with novel features. The lesion is distinct from the recently recognized focal gastritis of Crohn's disease, which is not CD8-dominated. As in the small intestine, there is epithelial deposition of IgG.

Rectal prolapse in autistic children. J Pediatr Surg. 2004 Apr;39(4):643-4.

Van Heest R, Jones S, Giacomantonio M.

Department of General Surgery, IWK Health Centre, Dalhousie University, Halifax, Nova Scotia, Canada.

Rectal prolapse in children is not uncommon, but surgery is rarely indicated. In mentally challenged adults and children, rectal prolapse occurs more frequently than in the general population and often requires surgical intervention in the second to third decade of life. The authors describe 3 children with autism and mental retardation who presented with rectal prolapse at an earlier age than would be anticipated with mental retardation alone. All 3 children required surgical intervention.

Food elimination based on IgG antibodies in irritable bowel syndrome: a randomised controlled trial. Gut. 2004 Oct;53(10):1459-64.

Atkinson W, Sheldon TA, Shaath N, Whorwell PJ.

Department of Medicine, University Hospital of South Manchester, Manchester M20 2LR, UK.

BACKGROUND: Patients with irritable bowel syndrome (IBS) often feel they have some form of dietary intolerance and frequently try exclusion diets. Tests attempting to predict food sensitivity in IBS have been disappointing but none has utilised IgG antibodies. **AIMS:** To assess the therapeutic potential of dietary elimination based on the presence of IgG antibodies to food. **PATIENTS:** A total of 150 outpatients with IBS were randomised to receive, for three months, either a diet excluding all foods to which they had raised IgG antibodies (enzyme linked immunosorbant assay test) or a sham diet excluding the same number of foods but not those to which they had antibodies. **METHODS:** Primary outcome measures were change in IBS symptom severity and global rating scores. Non-colonic symptomatology, quality of life, and anxiety/depression were secondary outcomes. Intention to treat analysis was undertaken using a generalised linear model. **RESULTS:** After 12 weeks, the true diet resulted in a 10% greater reduction in symptom score than the sham diet (mean difference 39 (95% confidence intervals (CI) 5-72); $p = 0.024$) with this value increasing to 26% in fully compliant patients (difference 98 (95% CI 52-144); $p < 0.001$). Global rating also significantly improved in the true diet group as a whole ($p = 0.048$, NNT = 9) and even more in compliant patients ($p = 0.006$, NNT = 2.5). All other outcomes showed trends favouring the true diet. Relaxing the diet led to a 24% greater deterioration in symptoms in those on the true diet (difference 52 (95% CI 18-88); $p = 0.003$). **CONCLUSION:** Food elimination based on IgG antibodies may be effective in reducing IBS symptoms and is worthy of further biomedical research.

Intestinal lymphocyte populations in children with regressive autism: evidence for extensive mucosal immunopathology. *J Clin Immunol.* 2003 Nov;23(6):504-17.

Ashwood P, Anthony A, Pellicer AA, Torrente F, Walker-Smith JA, Wakefield AJ.

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Inflammatory intestinal pathology has been reported in children with regressive autism (affected children). Detailed analysis of intestinal biopsies in these children indicates a novel lymphocytic enterocolitis with autoimmune features; however, links with cognitive function remain unclear. To characterize further, the nature and extent of this disease we examined the mucosal infiltrate using flow cytometry. Duodenal, ileal, and colonic biopsies were obtained from 52 affected children, 25 histologically normal, and 54 histologically inflamed, developmentally normal controls. Epithelial and lamina propria lymphocyte populations were isolated and examined by multicolor flow cytometry. Adjacent biopsies were assessed by semiquantitative histopathology. At all sites, CD3(+) and CD3(+)CD8(+) IEL as well as CD3(+) LPL were significantly increased in affected children compared with developmentally normal noninflamed control groups ($p < 0.01$) reaching levels similar to inflamed controls. In addition, two populations--CD3(+)CD4(+) IEL and LP CD19(+) B cells--were significantly increased in affected children compared with both noninflamed and inflamed control groups including IBD, at all sites examined ($p < 0.01$). Histologically there was a prominent mucosal eosinophil infiltrate in affected children that was significantly lower in those on a gluten- and casein-free diet, although lymphocyte populations were not influenced by diet. The data provide further evidence of a pan-enteric mucosal immunopathology in children with regressive autism that is apparently distinct from other inflammatory bowel diseases.

White JF.: Intestinal pathophysiology in autism. *Exp Biol Med* (Maywood). 2003 Jun;228(6):639-49.

Summary:

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Autism is a life-long developmental disorder affecting as many as 1 in 500 children. The causes for this profound disorder are largely unknown. Recent research has uncovered pathology in the gastrointestinal tract of autistic children. The pathology, reported to extend from the esophagus to the colon, is described here along with other studies pointing to a connection between diet and the severity of symptoms expressed in autism. The evidence that there is impaired intestinal permeability in autism is reviewed, and various theories are discussed by which a leaky gut could develop. Lastly, some possible ways in which impaired gastrointestinal function might influence brain function are discussed. [FULL TEXT ARTICLE](#)

Afzal N, Murch S, Thirupathy K, Berger L, Fagbemi A, Heuschkel R: Constipation with acquired megarectum in children with autism. *Pediatrics.* 2003 Oct;112(4):939-42.

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OBJECTIVE: Recent evidence suggests that autistic children may have significant gastrointestinal symptoms. Although constipation occurs in 2% to 5% of healthy children, its clinical diagnosis is often difficult in children with behavioral disorders. We thus aimed to assess the prevalence of fecal loading in autistic children with gastrointestinal symptoms and to identify possible predictors of constipation. **METHODS:** We studied abdominal radiographs of 103 autistic children (87 boys) who were referred for gastroenterological assessment, in comparison with 29 control radiographs from children who were referred to the emergency department, most with abdominal pain. Radiographs were scored independently, in blinded manner, by 4 pediatric gastroenterologists and a radiologist. The severity of constipation was determined using a validated index. Details of stool habit, abdominal pain, dietary history, and laxative use were obtained from case notes. **RESULTS:** The incidence of constipation in the control subjects with abdominal pain was higher than reported for normal children. Despite this, moderate or severe constipation was more frequent in the autistic group than in the control subjects (36% vs 10%). Analysis of rectosigmoid loading showed more striking differences (54.4% of autistic children had moderate/severe loading or acquired megarectum compared with 24.1% of control subjects). Multivariate regression analysis showed consumption of milk to be the

strongest predictor of constipation in the autistic group, whereas stool frequency, gluten consumption, soiling, and abdominal pain were not predictive of constipation. **CONCLUSIONS:** Constipation is a frequent finding in children with gastrointestinal symptoms and autism, particularly in the rectosigmoid colon, often with acquired megarectum. The absence of any correlation between the clinical history and the degree of fecal impaction in autistic children confirms the importance of an abdominal radiograph in the assessment of their degree of constipation.

Welch MG, Keune JD, Welch-Horan TB, Anwar N, Anwar M, Ruggiero DA.: Secretin activates visceral brain regions in the rat including areas abnormal in autism. *Cell Mol Neurobiol.* 2003 Oct;23(4-5):817-37.

Abstract:

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1. The aim of this study was to determine whether central networks are involved in the presumptive behavioral and autonomic regulatory actions of secretin, a gut hormone that has been reported to have ameliorative effects in autistic children. 2. Central neural responses monitored by regional c-fos gene expression were examined in response to intracerebroventricular secretin injection in awake, freely-moving Sprague-Dawley rats. Tissue sections were incubated in an antibody to the c-fos gene product, Fos, and processed immunohistochemically. 3. Qualitative differences in Fos immunoreactivity in stress adaptation and visceral representation areas of the brain were observed between secretin- and vehicle-infused age-matched pairs (n = 4 pairs). Secretin-activated regions include the area postrema, dorsal motor nucleus, medial region of the nucleus of the solitary tract and its relay station in the lateral tegmentum, locus ceruleus, ventral periaqueductal gray, periventricular thalamic nucleus, paraventricular hypothalamus magnocellularis, medial and central amygdala, lateral septal complex as well as ependymal and subependymal nuclei lining the third ventricle. Specific areas of the cerebral cortex were heavily labeled in secretin-treated rats, as compared to controls: the medial bank of the anterior prefrontal cortex, orbitofrontal cortex, the piriform cortex, and the anterior olfactory nucleus. Secretin attenuated Fos immunoreactivity in the dorsal periaqueductal gray, intralaminar thalamus, medial parvocellular compartment of the hypothalamus, supraoptic nucleus of the hypothalamus, lateral amygdala, motor cortex, and the somatosensory and association areas of the parietal cortex. 4. Secretin alters the activity of structures involved in behavioral conditioning of stress adaptation and visceral reflex reactions. This study predicts a possible cellular mechanism, activation of third ventricular ependymal and subependymal cells, as well as central regulatory actions of secretin. The physiological effects of secretin on behavioral, endocrine, autonomic and sensory neuronal activation patterns, together, contribute to central c-fos activation. Secretin alters the activity of structures involved in behavioral conditioning of stress adaptation and visceral reflex reactions. This study predicts a possible cellular mechanism, activation of third ventricular ependymal and subependymal cells, and central regulatory actions of secretin. The physiological effects of secretin on behavioral, endocrine, autonomic and sensory neuronal activation patterns, together, contribute to central c-fos activation. **These findings mandate further investigation of secretin as a brain/gut stress regulatory hormone.**

Latham F, Merino F, Lang A, Garvey J, Thomson MA, Walker-Smith JA, Davies SE, Phillips AD, Murch SH: A consistent pattern of minor immunodeficiency and subtle enteropathy in children with multiple food allergy. *J Pediatr.* 2003 Jul;143(1):39-47.

Centre for Paediatric Gastroenterology and Department of Dietetics and Histopathology, Royal Free and University College School of Medicine, London, United Kingdom.

OBJECTIVE: Although immunoglobulin (Ig)E-mediated allergies are readily identifiable, non-IgE-mediated allergies present more diagnostic difficulty. We performed a formal retrospective analysis to determine whether there is a recognizable clinical pattern in children. **METHODS:** We studied 121 children (mean age, 17.3 months) with multiple food allergies who were recruited on the basis of adequate immunological assessment by using case notes and parental questionnaire. **RESULTS:** Group 1 (n=44) had rapid reactions to dietary antigens, of whom 41 also showed delayed reactions. Group 2 (n=77) had delayed reactions only. Mean IgE was increased in group 1 but both groups otherwise shared a pattern of increased IgG1, decreased IgG2/4, and low-normal IgA. Lymphocyte subsets were skewed, with an increased percentage of CD4 and CD19 and decreased CD8 and natural killer cells. Gastroesophageal reflux, esophagitis, subtle enteropathy, and constipation were frequent in both groups. Of 55 exclusively breast-fed infants, 44 sensitized before weaning. Twenty-one of the mothers suffered from autoimmunity. **CONCLUSIONS:** There appears to be a recognizable pattern of immune deviation and minor enteropathy in children with multiple food allergy, irrespective of the speed of reactions. Disturbed gut motility is particularly common, as is

a maternal history of autoimmunity.

Molloy CA, Manning-Courtney P.: Prevalence of chronic gastrointestinal symptoms in children with autism and autistic spectrum disorders. *Autism.* 2003 Jun;7(2):165-71.

Abstract:

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The purpose of this study was to estimate the prevalence of chronic gastrointestinal symptoms in a general population of children with autism or autistic spectrum disorder (ASD). The study site was a clinic specializing in ASD in a large pediatric medical center serving a 10 county area in the midwestern USA. In a sample of 137 children, age 24-96 months, classified as having autism or ASD by the Autism Diagnostic Observation Schedule-Generic, 24 percent had a history of at least one chronic gastrointestinal symptom. The most common symptom was diarrhea, which occurred in 17 percent. There was no association between chronic gastrointestinal symptoms and a history of developmental regression. The potential phenotypic association between autism and gastrointestinal symptoms is discussed.

Buie T, Winter H, Kushak, R: Preliminary findings in gastrointestinal investigation of autistic patients. 2002.

Summary:

Harvard University and Mass General Hospital , <http://www.ladders.org/autism.php>

111 patients evaluated, ages 14 Months to 20 Years, all with GI symptoms of pain or diarrhea. Endoscopic findings: Esophagitis in 23 (20%), Gastritis in 14 (12%); 4 had Helicobacter pylori; Duodenitis in 11 (10%); 2 had Celiac Sprue; Eosinophilic Inflammation in 5 (5%). 10 out of 90 tested (11%) had unusually low enzyme activity: 2 with total pancreatic insufficiency and 5 with multiple enzyme defects. Lactase deficiency was found in 55% of ASD children tested, and combined deficiency of disaccharidase enzymes was found in 15%. Enzyme assays correlate well with hydrogen breath tests. Colitis was found in 11 of 89 patients (12%), none with features of Ulcerative Colitis or Crohn's. Histologic (biopsy reviewed) lymphoid nodular hyperplasia was found in 15 of 89 patients (16%). Eosinophilic inflammation was found in 13 of 89 patients (14%); cause or significance is unclear. Conclusions: more than 50% of autistic children appear to have GI symptoms, food allergies, and maldigestion or malabsorption issues. We need large, evidence-based studies need to be done in order to fully understand the gut-brain association in autism.

Krigsman, A, et al: Preliminary data presented at congressional hearing. 2002 Jun.

Summary:

New York University School of Medicine: www.med.nyu.edu

We examined 43 patients with autism, in whom we demonstrated enterocolitis in 65% and terminal ileal LNH in 90%. As of November, 2002, our total patient population now stands at 82, and the percentages of enterocolitis and LNH are essentially unchanged. Additional studies will follow.

Finegold SM, Molitoris D, Song Y, Liu C, Vaisanen ML, Bolte E, McTeague M, Sandler R, Wexler H, Marlowe EM, Collins MD, Lawson PA, Summanen P, Baysallar M, Tomzynski TJ, Read E, Johnson E, Rolfe R, Nasir P, Shah H, Haake DA, Manning P, Kaul A: Gastrointestinal microflora studies in late-onset autism. Clin Infect Dis. 2002 Sep 1;35(Suppl 1):S6-S16.

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Some cases of late-onset (regressive) autism may involve abnormal flora because oral vancomycin, which is poorly absorbed, may lead to significant improvement in these children. Fecal flora of children with regressive autism was compared with that of control children, and clostridial counts were higher. The number of clostridial species found in the stools of children with autism was greater than in the stools of control children. Children with autism had 9 species of Clostridium not found in controls, whereas controls yielded only 3 species not found in children with autism. In all, there were 25 different clostridial species found. In gastric and duodenal specimens, the most striking finding was total absence of non-spore-forming anaerobes and microaerophilic bacteria from control children and significant numbers of such bacteria from children with autism. These studies demonstrate significant alterations in the upper and lower intestinal flora of children with late-onset autism and may provide insights into the nature of this disorder.

Wakefield AJ, Puleston JM, Montgomery SM, Anthony A, O'Leary JJ, Murch SH: Review article: the concept of enterocolonic encephalopathy, autism and opioid receptor ligands. Aliment Pharmacol Ther 2002 Apr;16(4):663-74.

Abstract:

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There is growing awareness that primary gastrointestinal pathology may play an important role in the inception and clinical expression of some childhood developmental disorders, including autism. In addition to frequent gastrointestinal symptoms, children with autism often manifest complex biochemical and immunological abnormalities. The gut-brain axis is central to certain encephalopathies of extra-cranial origin, hepatic encephalopathy being the best characterized. Commonalities in the clinical characteristics of hepatic encephalopathy and a form of autism associated with developmental regression in an apparently previously normal child, accompanied by immune-mediated gastrointestinal pathology, have led to the proposal that there may be analogous mechanisms of toxic encephalopathy in patients with liver failure and some children with autism. Aberrations in opioid biochemistry are common to these two conditions, and there is evidence that opioid peptides may

mediate certain aspects of the respective syndromes. The generation of plausible and testable hypotheses in this area may help to identify new treatment options in encephalopathies of extra-cranial origin. Therapeutic targets for this autistic phenotype may include: modification of diet and entero-colonic microbial milieu in order to reduce toxin substrates, improve nutritional status and modify mucosal immunity; anti-inflammatory/immunomodulatory therapy; and specific treatment of dysmotility, focusing, for example, on the pharmacology of local opioid activity in the gut.

Uhlmann V, Martin CM, Sheils O, Pilkington L, Silva I, Killalea A, Murch SB, Walker-Smith J, Thomson M, Wakefield AJ, O'Leary JJ: Potential viral pathogenic mechanism for new variant inflammatory bowel disease. *Mol Pathol* 2002 Apr;55(2):84-90

Abstract:

Department of Pathology, Coombe Women's Hospital, Dublin 8, Ireland .

AIMS: A new form of inflammatory bowel disease (ileocolonic lymphonodular hyperplasia) has been described in a cohort of children with developmental disorder. This study investigates the presence of persistent measles virus in the intestinal tissue of these patients (new variant inflammatory bowel disease) and a series of controls by molecular analysis. **METHODS:** Formalin fixed, paraffin wax embedded and fresh frozen biopsies from the terminal ileum were examined from affected children and histological normal controls. The measles virus Fusion (F) and Haemagglutinin (H) genes were detected by TaqMan reverse transcription polymerase chain reaction (RT-PCR) and the Nucleocapsid (N) gene by RT in situ PCR. Localisation of the mRNA signal was performed using a specific follicular dendritic cell antibody. **RESULTS:** Seventy five of 91 patients with a histologically confirmed diagnosis of ileal lymphonodular hyperplasia and enterocolitis were positive for measles virus in their intestinal tissue compared with five of 70 control patients. Measles virus was identified within the follicular dendritic cells and some lymphocytes in foci of reactive follicular hyperplasia. The copy number of measles virus ranged from one to 300,00 copies/ng total RNA. **CONCLUSIONS:** The data confirm an association between the presence of measles virus and gut pathology in children with developmental disorder.

Torrente F, Ashwood P, Day R, Machado N, Furlano RI, Anthony A, Davies SE, Wakefield AJ, Thomson MA, Walker-Smith JA, Murch SH: Small intestinal enteropathy with epithelial IgG and complement deposition in children with regressive autism. *Mol Psychiatry* 2002;7(4):375-82, 334

Abstract:

Centre for Paediatric Gastroenterology, Royal Free & University College Medical School , London , UK .

We have reported lymphocytic colitis in children with regressive autism, with epithelial damage prominent. We now compare duodenal biopsies in 25 children with regressive autism to 11 with coeliac disease, five with cerebral palsy and mental retardation and 18 histologically normal controls. Immunohistochemistry was performed for lymphocyte and epithelial lineage and functional markers. We determined the density of intraepithelial and lamina propria lymphocyte populations, and studied mucosal immunoglobulin and complement C1q localisation. Standard histopathology showed increased enterocyte and Paneth cell numbers in the autistic children. Immunohistochemistry demonstrated increased lymphocyte infiltration in both epithelium and lamina propria with upregulated crypt cell proliferation, compared to normal and cerebral palsy controls. Intraepithelial lymphocytes and lamina propria plasma cells were lower than in coeliac disease, but lamina propria T cell populations were higher and crypt proliferation similar. Most strikingly, IgG deposition was seen on the basolateral epithelial surface in 23/25 autistic children, co-localising with complement C1q. This was not seen in the other conditions. These findings demonstrate a novel form of enteropathy in autistic children, in which increases in mucosal lymphocyte density and crypt cell proliferation occur with epithelial IgG deposition. The features are suggestive of an autoimmune lesion.

Wakefield AJ, Puleston JM, Montgomery SM, Anthony A, O'Leary JJ, Murch SH: Review article: the concept of entero-colonic encephalopathy, autism and opioid receptor ligands. *Aliment Pharmacol Ther.* 2002 Apr;16(4):663-74.

Inflammatory Bowel Disease Study Group, Centre for Gastroenterology, Department of Medicine, Royal Free and University College Medical School, London, UK. wakers@aol.com

There is growing awareness that primary gastrointestinal pathology may play an important role in the inception and clinical expression of some childhood developmental disorders, including autism. In addition to frequent gastrointestinal symptoms, children with autism often manifest complex biochemical and immunological abnormalities. The gut-brain axis is central to certain encephalopathies of extra-cranial origin, hepatic encephalopathy being the best characterized. Commonalities in the clinical characteristics of hepatic encephalopathy and a form of autism associated with developmental regression in an apparently previously normal child, accompanied by immune-mediated gastrointestinal pathology, have led to the proposal that there may be analogous mechanisms of toxic encephalopathy in patients with liver failure and some children with autism. Aberrations in opioid biochemistry are common to these two conditions, and there is evidence that opioid peptides may mediate certain aspects of the respective syndromes. The generation of plausible and testable hypotheses in this area may help to identify new treatment options in encephalopathies of extra-cranial origin. Therapeutic targets for this autistic phenotype may include: modification of diet and entero-colonic microbial milieu in order to reduce toxin substrates, improve nutritional status and modify mucosal immunity; anti-inflammatory/immunomodulatory therapy; and specific treatment of dysmotility, focusing, for example, on the pharmacology of local opioid activity in the gut.

Furlano RI, Anthony A, Day R, Brown A, McGarvey L, Thomson MA, Davies SE, Berelowitz M, Forbes A, Wakefield AJ, Walker-Smith JA, Murch SH: Colonic CD8 and gamma delta T-cell infiltration with epithelial damage in children with autism. *J Pediatr* 2001 Mar;138(3):366-72.

Abstract:

University Department of Paediatric Gastroenterology, the Inflammatory Bowel Diseases Study Group, Royal Free and University College School of Medicine, London, United Kingdom.

OBJECTIVES: We have reported colitis with ileal lymphoid nodular hyperplasia (LNH) in children with regressive autism. The aims of this study were to characterize this lesion and determine whether LNH is specific for autism. **METHODS:** Ileocolonoscopy was performed in 21 consecutively evaluated children with autistic spectrum disorders and bowel symptoms. Blinded comparison was made with 8 children with histologically normal ileum and colon, 10 developmentally normal children with ileal LNH, 15 with Crohn's disease, and 14 with ulcerative colitis. Immunohistochemistry was performed for cell lineage and functional markers, and histochemistry was performed for glycosaminoglycans and basement membrane thickness. **RESULTS:** Histology demonstrated lymphocytic colitis in the autistic children, less severe than classical inflammatory bowel disease. However, basement membrane thickness and mucosal gamma delta cell density were significantly increased above those of all other groups including patients with inflammatory bowel disease. CD8(+) density and intraepithelial lymphocyte numbers were higher than those in the Crohn's disease, LNH, and normal control groups; and CD3 and plasma cell density and crypt proliferation were higher than those in normal and LNH control groups. Epithelial, but not lamina propria, glycosaminoglycans were disrupted. However, the epithelium was HLA-DR(-), suggesting a predominantly T(H)2 response. **INTERPRETATION:** Immunohistochemistry confirms a distinct lymphocytic colitis in autistic spectrum disorders in which the epithelium appears particularly affected. This is consistent with increasing evidence for gut epithelial dysfunction in autism.

Wakefield AJ, Anthony A, Murch SH, Thomson M, Montgomery SM, Davies S, O'Leary JJ, Berelowitz M, Walker-Smith JA: Enterocolitis in children with developmental disorders. *Am J Gastroenterol.* 2000 Sep;95(9):2285-95. University Department of Medicine, Royal Free and University College Medical School, London, United Kingdom.

OBJECTIVE: Intestinal pathology, i.e., ileocolonic lymphoid nodular hyperplasia (LNH) and mucosal inflammation, has been described in children with developmental disorders. This study describes some of the endoscopic and pathological characteristics in a group of children with developmental disorders (affected children) that are associated with behavioral regression and bowel symptoms, and compares them with pediatric controls. **METHODS:** Ileocolonoscopy and biopsy were performed on 60 affected children (median age 6 yr, range 3-16; 53 male). Developmental diagnoses were autism (50 patients), Asperger's syndrome (five), disintegrative disorder (two), attention deficit hyperactivity disorder (ADHD) (one), schizophrenia (one), and dyslexia (one). Severity of ileal LNH was graded (0-3) in both affected children and 37 developmentally normal controls (median age 11 yr, range 2-13 yr) who were investigated for possible inflammatory bowel disease (IBD). Tissue sections were reviewed by three pathologists and scored on a standard proforma. Data were compared with ileocolonic biopsies from 22 histologically normal children (controls) and 20 children with ulcerative colitis (UC), scored in an identical manner. Gut pathogens were sought routinely. **RESULTS:** Ileal LNH was present in 54 of 58 (93%) affected children and in five of 35 (14.3%) controls ($p < 0.001$). Colonic LNH was present in 18 of 60 (30%) affected children and in two of 37 (5.4%) controls ($p < 0.01$). Histologically, reactive follicular hyperplasia was present in 46 of 52 (88.5%) ileal biopsies from affected children and in four of 14 (29%) with UC, but not in non-IBD controls ($p < 0.01$). Active ileitis was present in four of 51 (8%) affected children but not in controls. Chronic colitis was identified in 53 of 60 (88%) affected children compared with one of 22 (4.5%) controls and in 20 of 20 (100%) with UC. Scores of frequency and severity of inflammation were significantly greater in both affected children and those with UC, compared with controls ($p < 0.001$). **CONCLUSIONS:** A new variant of inflammatory bowel disease is present in this group of children with

developmental disorders.

Sandler RH, Finegold SM, Bolte ER, Buchanan CP, Maxwell AP, Vaisanen ML, Nelson MN, Wexler HM: Short-term benefit from oral vancomycin treatment of regressive-onset autism. *J Child Neurol.* 2000 Jul;15(7):429-35.

Section of Pediatric Gastroenterology and Nutrition, Rush Children's Hospital, Rush Medical College, Chicago, IL 60612, USA. rushstudy@aol.com

In most cases symptoms of autism begin in early infancy. However, a subset of children appears to develop normally until a clear deterioration is observed. Many parents of children with "regressive"-onset autism have noted antecedent antibiotic exposure followed by chronic diarrhea. We speculated that, in a subgroup of children, disruption of indigenous gut flora might promote colonization by one or more neurotoxin-producing bacteria, contributing, at least in part, to their autistic symptomatology. To help test this hypothesis, 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 pathophysiological insight and meaningful prevention or treatment in a subset of children with autism.

Kawashima H, Mori T, Kashiwagi Y, Takekuma K, Hoshika A, Wakefield A: Detection and sequencing of measles virus from peripheral mononuclear cells from patients with inflammatory bowel disease and autism. *Dig Dis Sci* 2000 Apr;45(4):723-9.

Abstract:

Department of Paediatrics, Tokyo Medical University, Japan.

It has been reported that measles virus may be present in the intestine of patients with Crohn's disease. Additionally, a new syndrome has been reported in children with autism who exhibited developmental regression and gastrointestinal symptoms (autistic enterocolitis), in some cases soon after MMR vaccine. It is not known whether the virus, if confirmed to be present in these patients, derives from either wild strains or vaccine strains. In order to characterize the strains that may be present, we have carried out the detection of measles genomic RNA in peripheral mononuclear cells (PBMC) in eight patients with Crohn's disease, three patients with ulcerative colitis, and nine children with autistic enterocolitis. As controls, we examined healthy children and patients with SSPE, SLE, HIV-1 (a total of eight cases). RNA was purified from PBMC by Ficoll-paque, followed by reverse transcription using AMV; cDNAs were subjected to nested PCR for detection of specific regions of the hemagglutinin (H) and fusion (F) gene regions. Positive samples were sequenced directly, in nucleotides 8393-8676 (H region) or 5325-5465 (from noncoding F to coding F region). One of eight patients with Crohn disease, one of three patients with ulcerative colitis, and three of nine children with autism, were positive. Controls were all negative. The sequences obtained from the patients with Crohn's disease shared the characteristics with wild-strain virus. The sequences obtained from the patients with ulcerative colitis and children with autism were consistent with being vaccine strains. The results were concordant with the exposure history of the patients. Persistence of measles virus was confirmed in PBMC in some patients with chronic intestinal inflammation.

Horvath K, Papadimitriou JC, Rabsztyrn A, Drachenberg C, Tildon JT: Gastrointestinal abnormalities in children with autistic disorder. *J Pediatr* 1999 Nov;135(5):559-63

Abstract:

Department of Pediatrics, University of Maryland School of Medicine, Baltimore, USA.

OBJECTIVES: Our aim was to evaluate the structure and function of the upper gastrointestinal tract in a group of patients with autism who had gastrointestinal symptoms. **STUDY DESIGN:** Thirty-six children (age: 5.7 +/- 2 years, mean +/- SD) with autistic disorder underwent upper gastrointestinal endoscopy with biopsies, intestinal and pancreatic enzyme analyses, and bacterial and fungal cultures. The most frequent gastrointestinal complaints were chronic diarrhea, gaseousness, and abdominal discomfort and distension. **RESULTS:** Histologic examination in these 36 children revealed grade I or II reflux esophagitis in 25 (69.4%), chronic gastritis in 15, and chronic duodenitis in 24. The number of Paneth's cells in the duodenal crypts was significantly elevated in autistic children compared with non-autistic control subjects. Low intestinal carbohydrate digestive enzyme activity was reported in 21 children (58.3%), although there was no abnormality found in pancreatic function. Seventy-five percent of the autistic children (27/36) had an increased pancreatico-biliary fluid output after intravenous secretin administration. Nineteen of the 21 patients with diarrhea had significantly higher fluid output than those without diarrhea. **CONCLUSIONS:** Unrecognized gastrointestinal disorders, especially reflux esophagitis and disaccharide malabsorption, may contribute to the behavioral problems of the non-verbal autistic patients. The observed increase in pancreatico-biliary secretion after secretin infusion suggests an upregulation of secretin receptors in the pancreas and liver. Further studies are required to determine the possible association between the brain and gastrointestinal dysfunctions in children with autistic disorder.

Wakefield AJ, Murch SH, Anthony A, Linnell J, Casson DM, Malik M, Berelowitz M, Dhillon AP, Thomson MA, Harvey P, Valentine A, Davies SE, Walker-Smith JA: Ileal-lymphoid-nodular hyperplasia, non-specific colitis, and pervasive developmental disorder in children. *Lancet* 1998 Feb 28;351(9103): 637-41

Abstract:

Inflammatory Bowel Disease Study Group, University Department of Medicine, Royal Free Hospital and School of Medicine, London, UK.

BACKGROUND: We investigated a consecutive series of children with chronic enterocolitis and regressive developmental disorder. **METHODS:** 12 children (mean age 6 years [range 3-10], 11 boys) were referred to a paediatric gastroenterology unit with a history of normal development followed by loss of acquired skills, including language, together with diarrhoea and abdominal pain. Children underwent gastroenterological, neurological, and developmental assessment and review of developmental records. Ileocolonoscopy and biopsy sampling, magnetic-resonance imaging (MRI), electroencephalography (EEG), and lumbar puncture were done under sedation. Barium follow-through radiography was done where possible. Biochemical, haematological, and immunological profiles were examined. **FINDINGS:** Onset of behavioural symptoms was associated, by the parents, with measles, mumps, and rubella vaccination in eight of the 12 children, with measles infection in one child, and otitis media in another. All 12 children had intestinal abnormalities, ranging from lymphoid nodular hyperplasia to aphthoid ulceration. Histology showed patchy chronic inflammation in the colon in 11 children and reactive ileal lymphoid hyperplasia in seven, but no granulomas. Behavioural disorders included autism (nine), disintegrative psychosis (one), and possible postviral or vaccinal encephalitis (two). There were no focal neurological abnormalities and MRI and EEG tests were

normal. Abnormal laboratory results were significantly raised urinary methylmalonic acid compared with age-matched controls ($p=0.003$), low haemoglobin in four children, and a low serum IgA in four children. INTERPRETATION: We identified associated gastrointestinal disease and developmental regression in a group of previously normal children, which was generally associated in time with possible environmental triggers.

D'Eufemia P., Celli M., Finocchiaro R., Pacifico L., Viozzi L., Zaccagnini M., Cardi E., Giardini O: Abnormal Intestinal Permeability in Children with Autism. *Acta Paediatrica*, 1996; 85: 1076-1079.

Abstract:

Institute of Pediatrics , La Sapienza University of Rome, Italy .

We determined the occurrence of gut mucosal damage using the intestinal permeability test in 21 autistic children who had no clinical and laboratory findings consistent with known intestinal disorders. An altered intestinal permeability was found in 9 of the 21 (43%) autistic patients, but in none of the 40 controls. Compared to the controls, these nine patients showed a similar mean mannitol recovery, but a significantly higher mean lactulose recovery ($1.64\% \pm 1.43$ vs $0.38\% \pm 0.14$; $P < 0.001$). **We speculate that an altered intestinal permeability could represent a possible mechanism for the increased passage through the gut mucosa of peptides derived from foods with subsequent behavioural abnormalities.**

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