Autism Insights

CASE REPORT

Clinical Presentation and Histologic Findings at Ileocolonoscopy in Children with Autistic Spectrum Disorder and Chronic Gastrointestinal Symptoms

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Abstract

Background: Children with developmental disorders experience chronic gastrointestinal symptoms.

Aims: To examine the nature of these gastrointestinal symptoms and histologic findings in children with autism spectrum/developmental disorders and ileocolonic disease.

Methods: Chart review. 143 autism spectrum/developmental disorder patients, with chronic gastrointestinal symptoms, undergoing diagnostic ileocolonoscopy.

Results: Diarrhea was present in 78%, abdominal pain in 59% and constipation in 36%. Ileal and/or colonic lymphonodular hyperplasia (LNH), defined as the presence of an increased number of enlarged lymphoid follicles, often with hyperactive germinal centers, was present in 73.2%. Terminal ileum LNH presented visually in 67% and histologically in 73%. Colonic LNH was multifocal and presented histologically in 32%. Ileal and/or colonic inflammation presented in 74%, consisting primarily of active or chronic colitis (69%). Ileal inflammation presented in 35%. Presence of LNH significantly predicted mucosal inflammation. Patients with ileal and/or colonic LNH had lower mean/median age than those without; patients with ileal and/or colonic inflammation had lower mean/median age than those without. There was a significant association between ileo and/or colonic inflammation or LNH, and onset of developmental disorder; plateaued or regressive onset conferred greater risk than early onset.

Conclusions: Patients with autism or related disorders exhibiting chronic gastrointestinal symptoms demonstrate ileal or colonic inflammation upon light microscopic examination of biopsy tissue. Further work is needed to determine whether resolution of histopathology with appropriate therapy is accompanied by GI symptomatic and cognitive/behavioral improvement.

Keywords: ASD ileitis, colitis, lymphonodular hyperplasia

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Introduction

Children with autism spectrum disorders (ASD) frequently have accompanying gastrointestinal (GI) symptoms[1–3] which may be intense, and directly impact quality of life. Valicenti-McDermott and colleagues[3] reported significant GI symptoms in 70% of an ASD cohort compared with 28% of children with typical development. In a prospective study, D'Souza and colleagues[4] documented GI symptoms in 80% of their ASD population. Similar proportions were reported by Melmed et al[5] and Horvath et al.[1] However, when compared with symptom prevalence of 8%–20% in ASD children based upon retrospective review of general practitioner (GP) records,[6–8] it is not surprising that the issue is controversial.[9]

Several published reports have detailed light microscopic and immunocytochemical findings of the stomach, small bowel, and colon in the ASD subset noting a non-specific enterocolitis, and excess proinflammatory cytokine production by mucosal T-cells and immune complex deposition.[10–18] We report on symptomatic presentation and histopathologic findings using light microscopy in 143 patients with ASD/developmental disorder, undergoing ileocolonoscopy and biopsy as part of routine investigations of persistent GI symptoms.

Materials and Methods

Subjects

Data review was conducted in accordance with Copernicus Group Institutional Review Board (IRB) oversight and protocol approval. All endoscopic examinations were clinically indicated and IRB approval was limited to retrospective review and compilation of findings using these procedures. Medical records were reviewed for 143 consecutive patients, with ASD or related diagnosis, referred for evaluation of chronic GI complaints, who underwent subsequent diagnostic ileocolonoscopy and biopsy for suspected bowel inflammatory disorders. Age, sex, developmental diagnosis, presenting gastrointestinal symptoms, and histopathologic findings were tabulated. Patients were referred either by primary care physicians or parents. Informed consent was obtained for each child included in the study.

Diarrhea was defined as persistent loose or unformed stool accounting for > = 50% of all bowel movements over 3 months prior to referral, unaffected by dietary interventions. Constipation was defined as any one of: (a) passage of < = 2 bowel movements per week, (b) hard or painful stools constituting the majority of bowel moments over the previous three months or (c) excessive difficulty in passing stool of any consistency.

Abdominal pain was easily determined in patients able to articulate discomfort. In non-verbal patients, abdominal pain was indicated by frequent, unexplained excessive irritability, awakening from sleep in a state of unusual irritability or agitation, and uncharacteristic aggression.[1] "Pain posturing", in which the child assumes a leaning position, providing direct pressure to the lower abdomen, is a clinically accepted pain indication in this population and parents were specifically asked about this. While initial patient evaluation included a dietary history to explore the possibility of food allergy, this was not a common finding. However, in virtually every case, foods causing non-IgE mediated GI symptoms were avoided for 6-months prior to endoscopic examination.

Laboratory investigations were tailored to presenting gastrointestinal symptoms and included complete blood count with differential, erythrocyte sedimentation rate and C-reactive protein, serum electrolytes, total protein and albumin, total serum IgA and tissue transglutaminase antibody, antigliadin IgA and IgG. Where appropriate, thyroid studies, growth hormone assay and abdominal imaging were obtained. Patients undergoing barium small bowel follow-through showed no evidence of stricture or stenosis. Stool was examined for bacterial and parasitic pathogens and presence of occult blood. In all cases, dietary interventions/restrictions did not significantly improve gastrointestinal symptomatology and initial laboratory evaluation did not provide an etiologic diagnosis. Patients refractory to conventional non-invasive management of gastrointestinal symptomotology underwent subsequent diagnostic ileocolonoscopy with mucosal biopsies. The specific indications for ileocolonoscopy were thus chronic diarrhea, constipation, and abdominal pain, either alone or in combination, that were (a) of unknown etiology, (b) refractory to conventional, noninvasive therapy and (c) significantly impacted quality of life. All colonoscopies were performed in the endoscopy unit of Lenox Hill Hospital, New York.

Three weeks prior to endoscopic procedures all patients refrained from taking medications that could

alter mucosal appearance, and micro-biologic agents capable of altering intestinal flora. The majority received bowel-prep comprising sodium phosphate (phosphosoda) with dosing based on age and weight. In children with history of severe constipation, polyethylene glycol solution (dosed according to age/weight) was ingested daily for 2 weeks prior to colonoscopy. Saline enemas were given the night before and morning of colonoscopy, and oral intake was limited to clear liquids for 24 hours prior to the procedure.

Relevant published reports describe primarily microscopic histopathology with subtle gross endoscopic findings; most patients therefore underwent multiple biopsies, targeting areas of subtle mucosal irregularity, and areas of healthy appearing mucosa. In most cases, biopsies were obtained in at least 6–8 colonic locations and 2–3 terminal ileal locations. Findings were taken from routine surgical pathology reports.

Routine surgical pathology reports were reviewed for presence/character of mucosal inflammatory activity. Particular attention was paid to the frequency with which the following descriptive terminology was employed: inflammation (chronic, acute, chronic active), cryptitis, and crypt abscess. Regarding the presence of hyperplastic lymphoid activity, the following descriptive terminology was recorded: reactive lymphoid hyperplasia, reactive lymphoid aggregates, reactive lymphoid follicles, nodular lymphoid hyperplasia, and lymphoid hyperplasia.

In order to determine whether patients with differing patterns of ASD onset had associated differences in pattern of bowel inflammation, the 143 patients were divided into three subgroups: a) normal development until at least age 12 m followed by loss of previously achieved developmental milestones prior to 24 m, accompanied by the appearance of typical autistic behaviors; b) normal development until at least age 12 m followed by developmental plateauing whereby milestones were not noticeably lost but development suffered marked deceleration, accompanied by appearance of typical autistic behaviors; and c) definite onset of autistic behaviors prior to age 12 m. It was hypothesized that this sub-grouping might uncover useful etiological information if differing patterns of clinical presentation reflected distinct disease entities.

Statistical analysis (SPSS 16.1)

Descriptive statistics provided means and standard deviations or median values and inter-quartile ranges (IQR) for normally and non-normally distributed continuous variables. Inferential statistics derived from cross-tabulation of categorical variables with chi-square statistics, asymptotic or exact probability levels and odds ratios with 95% confidence intervals. Non-parametric comparison of mean ranks (Mann-Whitney U) was used to evaluate group differences in age. When estimating prevalence of combined ileal versus colonic LNH/inflammation, the denominator included those patients successfully intubated in both the colon and terminal ileum (n = 127), unless otherwise stated. For estimates of association between ileal and or colonic pathology and other factors, all positively identified cases were included.

The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki (6th revision, 2008) as reflected in a priori approval by the institutions human research committee.

Results

Ages ranged from 12 m to 434 m (36 years, 2 months), mean age 76 m (SD 49) and median age 63 m (IQR 43). 122/143 (85.3%) were male. All but one subject were less than 220 m (18 yrs 4 months) of age.

Developmental diagnosis

136 (95.1%) patients had a diagnosis of autism, ASD, pervasive developmental disorder (PDD) or Asperger's syndrome. The remaining 7 (4.9%) had an unspecified developmental disorder. The developmental diagnosis was established by one or more of the following: pediatric neurologists, developmental pediatricians, pediatric psychiatrists, or psychologists. A clear history relating to onset of developmental disorder was obtained for 122 (85.3%) patients. Inflammation was not determined for specific subgroups of diagnoses.

Gastrointestinal symptoms

See Table 1 for frequencies of presenting gastrointestinal symptoms. The most common was diarrhea with 112 (78.3%) patients presenting either with diarrhea alone or in combination with constipation. Of these, 29 (25.9%) also had constipation, 83 (74%) did not. Constipation presented in 51 (35.7%) patients, of whom

Table 1. Frequency of gastrointestinal symptoms in 143 children undergoing ileocolonoscopy.

Gastrointestinal symptom	n	%
Diarrhea (alone)	83	58%
Constipation (alone)	22	15.4%
Diarrhea (alone, or in combination with constipation)	112	78.3%
Constipation (alone, or in combination with diarrhea)	51	35.7%
Both diarrhea and constipation	29	20.3%
Abdominal pain	85	59.4%
Abdominal distension	30	21.0%
Mucoid stool	27	18.9%
Hematochezia	11	7.7%

29 (56.9%) had accompanying diarrhea, 22 (43.1%) did not. Thus in the sample as a whole, 83 (58.0%) had diarrhea alone, 22 (15.4%) had constipation alone and 29 (20.3%) had both. Abdominal pain presented in 85 (59.4%). Abdominal distension presented in 30 cases (21%), mucoid stool in 27 (18.9%), and hematochezia in 11 (7.7%). No patients presented with clinical fistulae or bowel obstruction.

Inflammation

Ileal inflammation presented in 44 (34.6%) of 127 patients for whom ileal intubation was successful. Colonic inflammation presented in 99 (69.2%) of 143 patients. Of the 127 patients for whom ileal intubation was successful, inflammation in either the ileum or colon was identified in 94 patients (74.0%). However this fails to take account of an additional 11 patients whose biopsies demonstrated colonic inflammation but for whom ileal intubation was not successful. These 11 cases cannot form part of a new denominator as this would under-represent those for whom ileal intubation was not possible but whose colonic biopsy was negative for inflammation. Therefore, the overall prevalence estimate for ileal and or colonic inflammation in this sample ranges from 105/143 to 110/143 (73.4 to 76.9%). Inflammation in both the ileum and colon presented in 37 (29.1%) of 127 patients tested for both. Ileitis without accompanying colitis presented in 6 (4.7%) patients, whereas colitis without ileitis was seen in 50 (39.4%). Representative histologic ileitis and colitis are depicted in Figure 1 and is characterized by cryptitis and crypt branching, respectively.

Data for acute and/or chronic inflammation provide (a) an estimate of prevalence in the smaller sub-group for whom ileal intubation was successful followed by (b) a range estimated for the full sample in the same way as described above.

Acute inflammation in either the ileum or colon presented in 64 (50.4%) of 127 patients giving an overall prevalence for the full sample ranging from 73/143 to 80/143 (51.0%–55.9%). Chronic inflammation presented in 67 (52.8%) of 127 patients with an overall prevalence for the full sample ranging from 70/143 to 83/143 (49.0%–58.0%).

Inflammation of any type was distributed multifocally over the ileum and colon with no anatomic predilection (Table 2). Patients with colonic inflammation tended towards involvement of multiple anatomic sites.

Lymphoid Nodular Hyperplasia (LNH)

Ileal LNH was identified histologically in 93 (73.2%) and visually in 85 (66.9%) of 127 patients for whom ileal intubation was successful. Colonic LNH was observed in 46 (32.3%) of 143 patients. Representative endoscopic and histologic ileocolonic LNH are depicted in Figure 2 and were characterized by marked LNH of terminal ileum and colon with a hyperplastic germinal center and displacement of surface villi. LNH of either the ileum or colon was noted in 93 (73.2%) of 127 patients for whom ileal intubation was successful. This figure, however fails to take account of an additional 5 patients who tested positive for colonic LNH but for whom ileal intubation was not successful. Therefore the overall prevalence of LNH ranges from 98/143 to 109/143 (68.5%–76.2%). LNH of both the ileum and the colon was present in 40 (31.5%) of patients.

Histologically confirmed ileal LNH without colonic LNH was seen in 53 (41.7%) of 127 patients who tested for both while colonic LNH without histological ileal LNH was seen in only 1(0.79%) of these patients. LNH occurred more frequently in the ileum than the colon. Colonic LNH did not demonstrate anatomic predilection (Table 2). Many patients with colonic LNH had involvement of multiple sites.

Statistical analysis of the association between inflammation and LNH was carried out on the full sample of 143 subjects. Of the 98 patients who tested

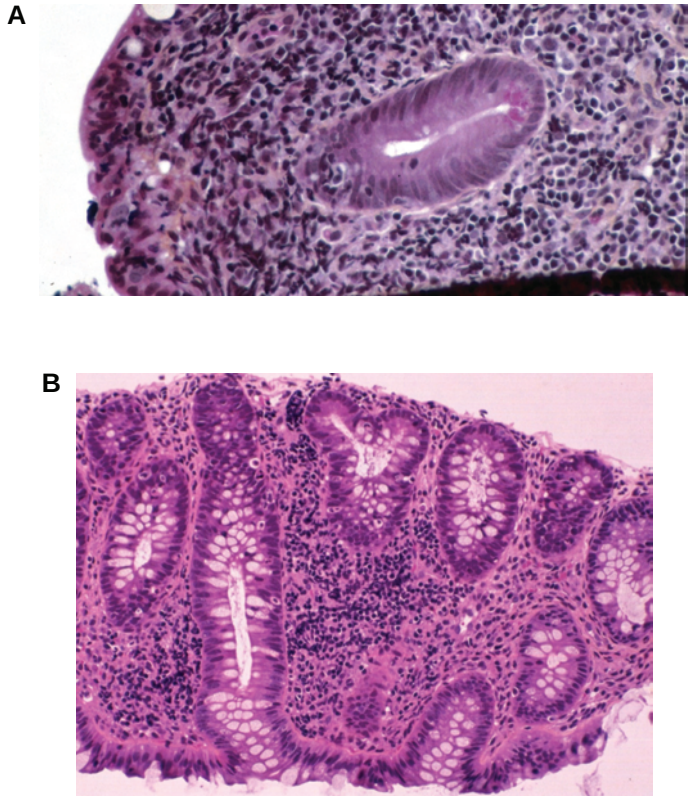

Figure 1. Representative images showing histologic ileitis and colitis. **A**) Acute and chronic ileitis with cryptitis (arrow). **B**) Focal chronic colitis with crypt branching (arrow) and patchy chronic inflammation associated with crypt architectural distortion.

positive for histologically confirmed ileal and/or colonic LNH, 78 (79.6%) had ileal and/or colonic inflammation compared to 20 (20.4%) who did not. Overall those with LNH were significantly more likely to be positive for inflammation with (chi-square 3.40, p = 0.04; OR 2.41; 95% CI 1.03–5.64).

Regional concordance between LNH and inflammation in the full sample reached statistical significance in the cecum where localized chronic inflammation was associated with LNH. Those with LNH of the cecum were approximately 3 times more likely to have localized chronic inflammation than those without (chi-square 4.38, p = 0.04; OR 3.02; 95% CI 1.04–8.82). Similarly, in the rectum localized acute inflammation was associated with LNH. Those with rectal LNH were approximately 3.5 times more likely to have localized acute inflammation than those without (chi-square 4.91, p = 0.03; OR = 3.48; 95% CI 1.10–11.03).

Generalized Linear Modelling (GLM) was used to examine the overall association between proportion of biopsies showing positive inflammation and overall LNH status. In a binary logistic main effects model, overall LNH status (Yes/No) was defined as outcome, with type of onset (regressive/plateaued versus early) as a between groups factor. Age and proportion of biopsies positive for inflammation were included as covariates. This analysis revealed significant main effects of age and type of onset, with younger children and regressive/plateaued onset increasing risk of LNH (Table 3). The proportion of biopsies with inflammation approached significance in this model. The model was significantly improved on an intercept-only model and the overall effect of onset type was also significant.

Association of histologic findings with constipation versus diarrhea

Inflammation

Of the 83 patients presenting with diarrhea without constipation, data on ileal and colonic inflammation was available for 74. Of these, 59 (79.7%) had inflammation in either the ileum, the colon or both locations. An additional 6 patients who presented with diarrhea but for whom ileal intubation was not successful, had colonic inflammation, while 3 did not. For patients presenting with diarrhea therefore, the estimate of prevalence of inflammation is between 65/83 and 68/83 (78.3%–81.9%). Data on ileal and colonic inflammation was available on 19 patients presenting with constipation without associated diarrhea. Of these, 12 (63.2%) had ileal or colonic inflammation. 3 patients for whom ileal intubation was not successful presented with diarrhea. All 3 had colonic inflammation. This allows a more definitive estimate of overall prevalence of inflammation in this group. Of the 22 patients presenting with constipation alone, 15 (68.1%) had ileal or colonic inflammation.

An examination of the association with inflammation for patients presenting with 'diarrhea only' or 'constipation only', found no statistically significant association, whether looking at acute, chronic, ileal or colonic inflammation.

LNH

Of the 74 patients presenting with diarrhea alone and for whom ileal intubation was successful, 56 (75.7%) had positive identification of histological LNH. An additional 3 patients for whom ileal intubation was not successful had colonic LNH, whilst 6 did not.

Table 2. Anatomical regions of the colon: Inflammation and LNH. Difference between denominators reflects the number of adequate biopsies taken from each site.

Region of bowel	No. of biopsies	Inflammation						LNH	
		Acute		Chronic		Both			
		n	%	n	%	n	%	n	%
Terminal Ileum	127	26	20.5	31	24.4	13	10.2	85	66.9
Cecum	135	28	20.7	29	21.5	12	8.9	17	12.6
Right colon	131	30	22.9	35	26.7	13	9.9	16	12.2
Hepatic	126	22	17.5	31	24.6	10	7.9	17	13.5
Transverse	139	28	20.1	39	28.1	12	8.6	21	15.1
Splenic	118	26	22.0	25	21.2	9	7.6	12	10.2
Left colon	126	33	26.2	27	21.4	11	8.7	14	11.1
Sigmoid	132	37	28.0	27	20.5	10	7.6	17	12.9
Rectum	138	28	20.3	27	19.6	8	5.8	14	10.1

For patients presenting with diarrhea therefore, the estimate of prevalence for LNH is between 59/83 and 65/83 (71.1%–78.3%). For the 22 patients presenting with constipation only, ileal intubation was successful in 19, and 14 (73.7%) of these had LNH. One additional 'constipation-only' patient for whom ileal intubation was not successful also had LNH while the remaining 2 did not. The range of prevalence of LNH in the 'constipation-only' group is therefore 15/22 to 17/22 (68.2%–77.3%).

When a variable was constructed to examine the association with LNH, between 'diarrhea-only' or 'constipation-only' groups, no statistically significant associations were found; 76.6% of the 'diarrhea-only' group had LNH compared to 75% of the 'constipation-only' group.

Colonic LNH was noted in 28 (33.7%) of the 'diarrhea-only' group and 6 (27.3%) of the 'constipation-only' group. Ileal LNH was noted in 56 (75.7%) of 74 'diarrhea—only' and 14 (73.7%) of the 19 'constipation-only' cases, for whom data were available. These were not significantly different proportions.

Effects of age and sex

Patients identified as having mucosal inflammation (colonic, ileal, acute or chronic) had a mean age of 69.9 m (SD 34.3) and a median age of 63 m (interquartile range [IQR] 35.5). Those without inflammation had a mean age of 82.2 m (SD 47.1) and a median age of 64 m (IQR 54.25) ($z = -1.24$, $p = 0.21$). The median age of patients with LNH (ileal, colonic, or both) was 63 m (IQR 36.50); those without LNH had a median age of 70 m (IQR 58). The difference approaches statistical significance ($z = -1.90$; $p = 0.06$) when constrained to those for whom status is available in both the ileum and colon. When children for whom ileal status is missing but colonic status is positive, are also included in the analysis as LNH 'positive' (rather than considered missing) the association reaches statistical significance ($z = -1.98$, $p = 0.048$) however, this introduces the issue of non-random missing data, as those for whom ileal status is unknown and colonic status is negative remain 'missing'. Furthermore, removal of the age-outlier (434 months) reduces the significance of this finding although p-values remain at <0.1. Positive colonic status may therefore be overrepresented in this particular analysis, potentially inflating the observed significance. Boys and girls had similar proportions of inflammation and LNH and no significant differences in anatomic distribution were noted between the sexes.

Discussion

This study confirms earlier reports of a non-specific (non-Crohn's disease, non-ulcerative colitis) mucosal histopathology in ASD patients with chronic gastrointestinal symptoms. It adds new information regarding the: (1) variety of gastrointestinal symptoms seen

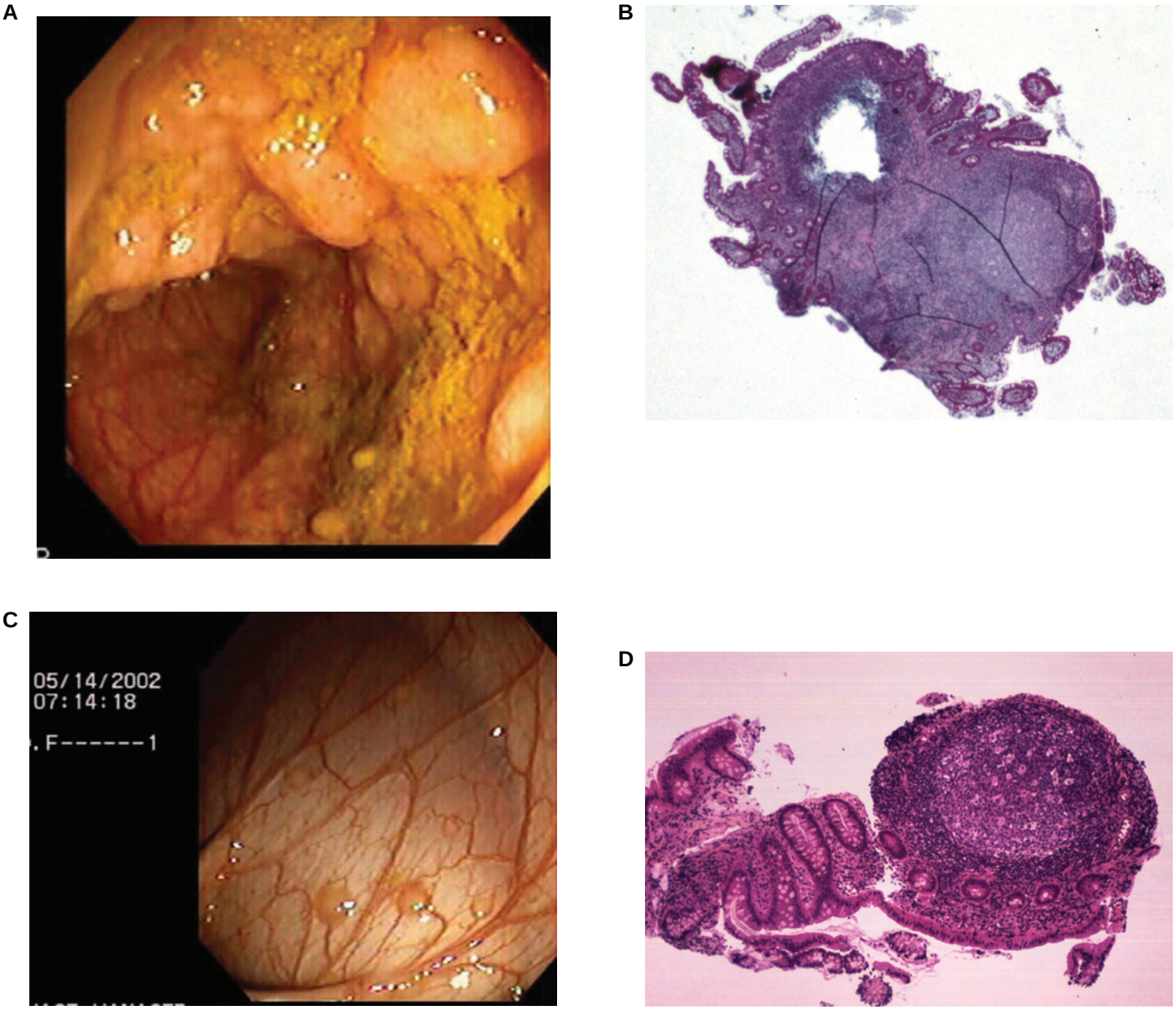

Figure 2. Gross endoscopic (**A**, **C**) and microscopic (**B**, **D**) appearance of characteristic terminal ileal LNH (top panel) and colonic LNH (lower panel). **A**) Marked LNH of terminal ileum (endoscopic). **B**) Microscopic appearance of A showing marked LNH of the terminal ileum. Note the hyperplastic germinal center and displacement of surface villi. **C**) Marked colonic LNH (endoscopic). **D**) Microscopic appearance of **C**. Note the hyperplastic germinal center with multiple tangible body macrophages (arrows).

in ASD patients in the presence of inflammation; (2) presence of multifocal anatomic distribution of inflammatory activity; and (3) significance of ileocolonic LNH in these children as an indication of accompanying inflammatory histopathology. As a case series, it does not seek to address issues of comparative surgical pathology and etiology; the finding of LNH and associated mucosal inflammation stands on its own in the absence of control groups.

It has long been observed by parents and clinicians that children with ASD are subject to chronic, often debilitating, gastrointestinal symptoms[1,2] and recent reports indicate an increased frequency of gastrointestinal symptoms in ASD children compared with appropriate age/sex matched neurotypical children and those with other developmental delays.[3] Numerous reports detail the histopathologic and immunohistochemical findings in the stomach,[13,14]

Table 3. GLM: logistic main effects model.

Factor/Covariate	Beta	SE	Wald	p
Type of onset	–1.45	0.68	4.52	0.033
Age in months	–0.01	0.01	4.02	0.044
Proportion biopsies inflammation	1.10	0.66	2.80	0.094
LR Chi-square for model fit	LR Chi-Sq = 13.25		df 3	0.004
Overall effect of onset type	Wald		df 1	0.042

proximal small bowel,[10,15,17] terminal ileum,[17,18] and colon[10,11,17,18] of these children. These reports demonstrate the consistent and anatomically diverse presence of mucosal lymphocyte infiltration, histological acute and chronic inflammation, γδ-delta T cells, eosinophils, and Paneth cells in the gastrointestinal mucosa of GI symptomatic ASD children compared with typically developing healthy controls without known gastrointestinal pathology. More recently, small bowel disease was reported in a GI symptomatic patient with regressive autism using wireless capsule endoscopy.[19] While the clinical significance of these findings remains unclear, no report exists to date suggesting the bowels of these children are normal. It appears that the immunologic and inflammatory activity in the bowel is part of a larger, systemic multi-organ immunopathology.[20–22]

Interpretation of the histopathologic findings in this study is best appreciated when viewed in the context of patient symptomatology. Indeed, it is this chronic symptomatology that is the clinical imperative for obtaining diagnostic biopsies. In this retrospective survey of 143 consecutive ASD patients with chronic gastrointestinal symptoms who underwent diagnostic colonoscopy, ileocolonic inflammation was present in the majority (76.1%), most of whom exhibited the coexisting presence of LNH.

While ileocolonic LNH has long been thought of as a 'normal' pediatric variant commonly encountered in developmentally normal children undergoing ileocolonoscopy, it is also a prominent component of the inflammatory response in gastrointestinal infectious processes such as *H. pylori gastritis*, *Shigellosis*, *C. difficile colitis*, and *yersiniosis*, among others. It is

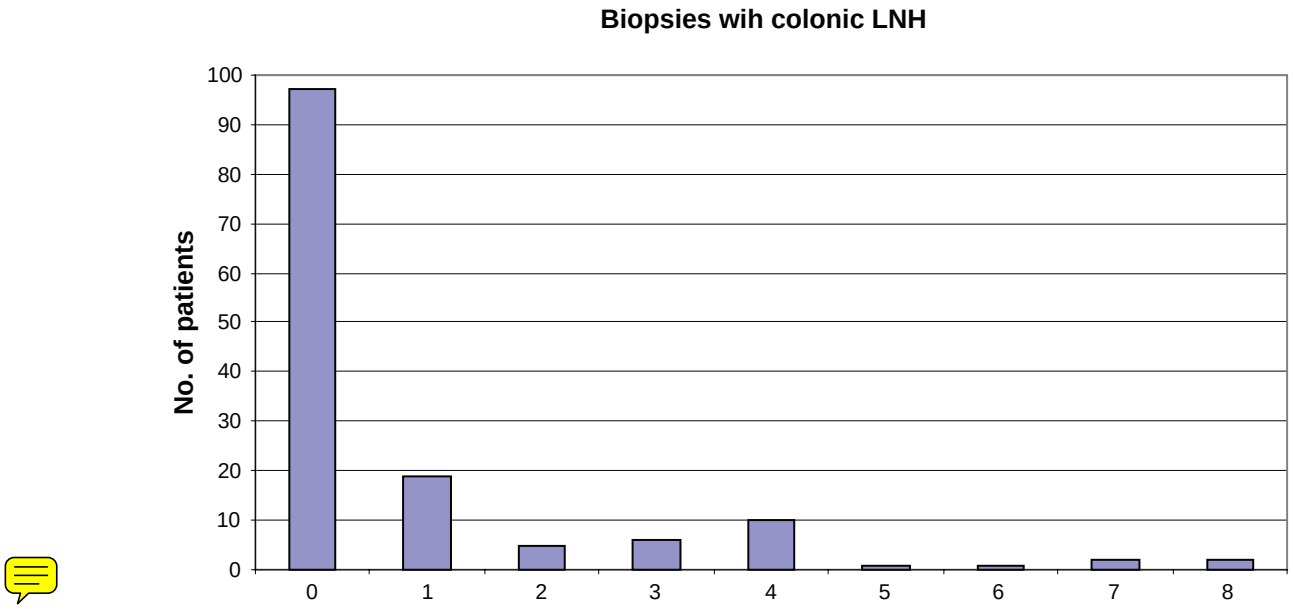

Figure 3. Frequency of multifocal LNH in 143 children. When present, colonic LNH tended to be multifocal.

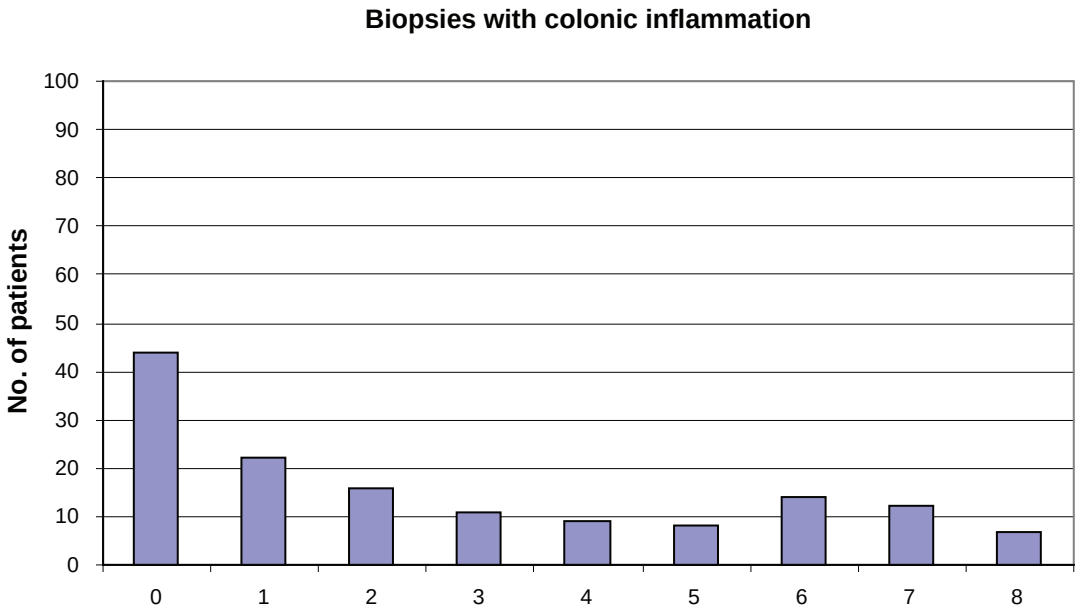

Figure 4. Frequency of multifocal colitis in 143 children. When present, colitis tended to be multifocal.

also a frequent coexisting feature in a constellation of presenting gastrointestinal signs and symptoms[23] and is an associated prominent finding in childhood inflammatory bowel disease.[24,25] Recent evidence suggests that it is likely associated with concurrent colonic immunopathology such as food allergy and colitis.[26] It was therefore hypothesized that presence of LNH in a symptomatic ASD cohort would be significant if associated with presence of ileocolonic inflammation. In this study, a statistically significant association between the two was noted; LNH of the terminal ileum and colon was predictive of ileocolonic inflammation. The LNH also tended to be diffusely present in the ileum and colon, consistent with known infectious and inflammatory processes of the bowel.

In order to determine whether the ileal and colonic histopathology (inflammation and LNH) represent true pathology rather than innocuous/non-specific variations from the norm, we sought to determine whether the ileocolonic histopathology (LNH or inflammation) tends to be unifocal or multifocal in individuals, and within the patient group. We found that ileitis, present in 35% of patients, was strongly associated with colonic inflammation and that colonic inflammation in the presence of ileitis tended to be multifocal. In addition, ileocolonic LNH was predictive of ileocolitis. Taken in the context of associated gastrointestinal symptomatology, these findings indicate that the combined observations of ileocolonic LNH and inflammation in this group of ASD patients may reflect genuine bowel pathology and should not be dismissed as a "normal" histologic variant.

An evaluation of the association between diarrhea and constipation revealed that 83 (58%) presented with diarrhea alone. Further analysis revealed that inflammation and LNH occurred with similar frequency in 'diarrhea-alone' and 'constipation-alone' groups, suggesting that, although chronic constipation has been postulated as a cause of ileocolonic inflammation in some children,[27] the mucosal inflammatory changes noted in this study cannot be ascribed to the effects of chronic constipation. The origin of the ileocolonic pathology is unknown. The pattern of inflammation may represent autoimmune disease, chronic infectious enterocolitis, food sensitivity/allergy, or a combination of the above. Because virtually all patients were on some form of a symptom-based restricted diet, the impact of specific dietary factors on symptoms and histopathology could not be evaluated in this study. Of additional interest was the finding that ASD-associated LNH and enterocolitis tended to occur in younger children. This confirms parental reports of more intense bowel symptoms in the toddler age-group, improving with age. Follow up studies are underway to determine the frequency with which celiac antibodies, celiac genetic markers, and

IBD serologic markers, are present in these children and whether their presence correlates with specific symptomatic disease variants.

Our analysis also found that a greater risk of bowel pathology was conferred by regression/plateau (developmental arrest) type onset than by early onset developmental delay. While the reason for this is not known, it may be speculated that the specific etiologic insult responsible for developmental arrest in a previously normally developing child is also responsible for the bowel inflammatory state, and this may be different from the etiologic agent responsible for developmental delay in the early onset group. Similar associations between developmental arrest, bowel inflammation, and known etiologic triggers have been described.[28–30]

This study constitutes an important step towards understanding the nature of gastrointestinal disease in children with ASDs. More work is necessary to clarify the etiology of this inflammation and its relationship to deficits of ASD.

Conflict of Interest Statement

Two of the authors AK and CS have acted as expert witnesses retained by claimant solicitors in vaccine related litigation. The first author (AK) is the treating physician retained by claimants in the US Omnibus Autism Proceeding. Neither AK nor CS considers this to constitute a real conflict of interest in relation to the current study.

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