AP&T Alimentary Pharmacology and Therapeutics

Review article: intestinal lymphoid nodular hyperplasia in children – the relationship to food hypersensitivity

P. Mansueto*, G. Iacono†, A. Seidita*, A. D'Alcamo*, D. Sprini* & A. Carroccio‡

*Internal Medicine, Policlinico University Hospital of Palermo, Palermo, Italy.
†Pediatric Gastroenterology, "Di Cristina" Hospital, Palermo, Italy.
‡Internal Medicine, Hospital of Sciacca, ASP Agrigento, Italy.

Correspondence to:
Dr P. Mansueto, Internal Medicine, Policlinico University Hospital of Palermo, via del Vespro 141, 90127 – Palermo, Italy.
E-mail: pasquale.mansueto@unipa.it

Publication data
Submitted 27 December 2011
First decision 18 January 2012
Resubmitted 22 February 2012
Accepted 24 February 2012
EV Pub Online 20 March 2012

This uncommissioned review article was subject to full peer-review.

SUMMARY

Background
Lymphoid aggregates are normally found throughout the small and large intestine. Known as lymphoid nodular hyperplasia (LNH), these aggregates are observed especially in young children and are not associated with clinical symptoms being considered 'physiological'. In children presenting with gastrointestinal symptoms the number and size of the lymphoid follicles are increased. Patients suffering from gastrointestinal symptoms (i.e. recurrent abdominal pain) should systematically undergo gastroduodenoscopy and colonoscopy. With these indications LNH, especially of the upper but also of the lower gastrointestinal tract has been diagnosed, and in some children it may reflect a food hypersensitivity (FH) condition.

Aim
To review the literature about the relationship between LNH and FH, particularly focusing on the diagnostic work-up for LNH related to FH.

Methods
We reviewed literature using Pubmed and Medline, with the search terms 'lymphoid nodular hyperplasia', 'food hypersensitivity', 'food allergy' and 'food intolerance'. We overall examined 10 studies in detail, selecting articles about the prevalence of LNH in FH patients and of FH in LNH patients.

Results
Collected data showed a median of 49% (range 32–67%) LNH in FH patients and a median of 66% (range 42–90%) FH in LNH patients. Literature review pointed out that the most important symptom connected with LNH and/or FH was recurrent abdominal pain, followed by diarrhoea and growth retardation. Both LNH and FH are associated with an increase in lamina propria $\gamma/\delta+$ T cells, but the mechanisms by which enhanced local immune responses causing gastrointestinal symptoms still remain obscure.

Conclusions
When assessing FH, we rely on clinical evaluation, including elimination diet and challenge tests, and endoscopic and immunohistochemical findings. Considering the possible co-existence of duodenal and ileo-colonic LNH, upper endoscopy can be recommended in children with suspected FH, especially in those presenting with additional upper abdominal symptoms (i.e. vomiting). Likewise, lower endoscopy might be additionally performed in patients with suspected FH and LNH of the duodenal bulb, also presenting with lower abdominal symptoms (i.e. recurrent abdominal pain).

Aliment Pharmacol Ther 2012; **35:** 1000–1009

doi:10.1111/j.1365-2036.2012.05062.x

LYMPHOID NODULAR HYPERPLASIA: FROM PHYSIOLOGY TO PATHOLOGY

Lymphoid follicles, with or without germinal centres, are normally found throughout the small and large intestine. In the terminal ileum these coalesce to form Peyer's patches. In the colon, the number of lymphoid structures increases from the caecum to the rectum. Lymphoid tissue is particularly prominent in the anorectal region, just above the dentate line of the anal canal.[1, 2] However, a high 'density' of lymphoid follicles could indicate a pathological condition. In this review, in accordance with previous published works, lymphoid nodular hyperplasia (LNH) was defined as a cluster of >10 extruding lymphoid nodules, whereas a lymphoid nodule was defined as an extruding lymphoid follicle with a diameter of $\geq$2 mm.[3]

In the gastrointestinal tract, the key step to antigen processing, evolving either into oral tolerance or a strong immune response against antigens administered orally, involves its initial uptake from the gut lumen by specialised follicle-associated epithelium called 'M' cells. M cells originate from adjacent crypt epithelium and are interspersed between the absorptive epithelial cells in the follicle-associated epithelium. These cells take up macromolecules, viruses, bacteria and protozoa within 30 min from the initial presentation of the antigen in the intestinal lumen. After the initial uptake of antigen by M cells, the antigens are transported into the follicular areas to be processed by dendritic cells and brought into close contact with the antigen-specific precursors for IgA-secreting plasma cells. The final result of M-cell processing is the production of a vigorous secretory IgA response and local cell-mediated immunity with suppression of a systemic IgG, IgE and delayed-type hypersensitivity to orally administered antigens.[4]

Lymphoid nodular hyperplasia presents endoscopically as smooth, yellow-white nodules up to 2 mm in diameter. They are observed more frequently in young children and are not associated with clinical symptoms, in which form LNH is considered to be 'physiological'. In children presenting with gastrointestinal symptoms, i.e. abdominal pain and rectal bleeding, the number and size of lymphoid follicles is increased and the anatomical distribution of enlarged lymphoid aggregates is age-dependent. It has been demonstrated that upper gastrointestinal symptoms in children could be related to food allergy. However, it is also known that the prevalence of food allergy declines with increasing age in adult life and this could be linked to the marked decrease in number of Peyer's patches and in LNH. In addition, adult subjects showing LNH at endoscopy examination have been reported to suffer more frequently from food allergy.[5]

Intestinal LNH has also been associated with viral and bacterial infection and immune deficiency status, thus it exists as both a physiological and as a pathological lesion.[6] For example, Khuroo *et al.* studied 40 patients with *Heliobacter pylori* and duodenal LNH. Video capsule endoscopies revealed nodular disease exclusively limited to the duodenum. Sequential antibiotic therapy eradicated *H. pylori* infection in 26 patients. Follow-up duodenoscopy in these patients showed a significant reduction in the duodenal nodular lesions score (i.e. complete resolution in five patients and significant resolution in the remaining 21 patients). The patients with resistant *H. pylori* infection showed no significant reduction in the nodular lesions score.[7] Finally, LNH is not always benign, and may be associated with intussusception[8] or even fatal colonic torsion.[9] Thus, acute onset abdominal pain in a child with documented LNH or intestinal food allergy should warrant early surgical assessment.

LNH AND FOOD HYPERSENSITIVITY

Food hypersensitivity (FH) is the umbrella term used to describe both food allergy, which involves the immune system (i.e. IgE and non-IgE-mediated mechanisms), as well as food intolerances, which do not.[10]

Food hypersensitivity may produce a wide variety of patchy or diffuse mucosal lesions in any part of the gastrointestinal tract, depending on the genetic characteristics of the subject and the type of the intervening immunological reaction. The changes may manifest clinically as buccal rash, aphthous wounds of the oral cavity, gastro-oesophageal reflux or oesophagitis, gastritis in the stomach, villous atrophy in the small intestine or colitis and may finally appear as an itchy rash around the anus. Although most of the lesions are limited to certain areas, the changes may occasionally spread throughout the whole gastrointestinal tract, a condition which is very often characterised by eosinophilic mucosal infiltrate and is termed 'eosinophilic gastroenteropathy'.[11, 12]

Food hypersensitivity in infants is more often generalised, with symptoms of dermatitis and/or mucosal reactions of the respiratory tract to corresponding allergies. In school-age children or adults, in whom gastrointestinal symptoms are more prominent, symptoms vary from malabsorption with loose stools or growth retardation and anaemia, to regurgitation, discomfort and abdominal pain and constipation.[13]

The diagnosis is nowadays based on elimination diets and on repeated open oral provocation tests, but the 'gold diagnostic standard' is the double-blind placebo-controlled challenge.[14]

As most subjects with FH are examined only for the main and more severe symptoms, the overall extent and macroscopic and histological characteristics of the related lesions have often remained obscure. In particular, infants and children with FH have not been systematically scheduled for endoscopic examination. Knowledge of mucosal abnormalities has been based on small intestinal biopsies from limited selected patient series. Colonoscopy has also been indicated in selected patients with severe chronic or recurrent abdominal pain, or presenting with chronic constipation refractory to laxative therapy or blood in stools. With these indications LNH, especially of the mucosa of the upper gastrointestinal tract (i.e. duodenal bulb), has been diagnosed and in some children it may reflect a condition of overt FH. On the other hand, it must be underlined that in most of these studies, the diagnosis of FH was not properly managed (nonblinded, not placebo-controlled). However, previous reports have demonstrated this lesion in patients without FH, presenting with common variable immunodeficiency, hypogammaglobulinaemia, IgA deficiency, HIV infection, HP infection, giardiasis, juvenile idiopathic arthritis and connective tissue disease or intestinal malignant lymphoma, as well as in healthy subjects.[15–23]

LNH OF THE DUODENAL BULB

Some studies have demonstrated a significant association between FH and LNH distributed diffusely on the duodenal bulb. Lymphoid nodules on the duodenal mucosa are distinctly more numerous in subjects with FH than in patients in whom any other state or coeliac disease is diagnosed. FH in duodenal LNH subjects was mostly of the gastrointestinal type. Even at onset it manifested with symptoms of vomiting or recurrent abdominal pain, and after oral challenge gastrointestinal symptoms were the first to be manifested, although in some patients dermatitis was exacerbated later on. Moreover, in most duodenal LNH patients it is not possible to demonstrate atopic allergy by skin prick tests or elevated serum IgE values. Thus, the patients with duodenal bulb LNH mostly present a local reactivity of delayed-type FH.[15, 16]

It has been also demonstrated that an intensive humoral immune response to cow's milk proteins and their fractions may be associated with gastrointestinal symptoms (i.e. recurrent abdominal pain) and duodenal LNH, even in children over the age of 3 years. Endoscopic findings in these patients included local and patchy hyperplasia of the lymphoid tissue and immunological evidence showed that the untreated cow's milk allergy children had significantly higher levels of IgA and IgG class antibodies to whole cow's milk and its specific fractions than age-matched controls.[24]

Cow's milk allergy can also exist in school-age children. Moreover, there is increasing evidence that this allergy may also be a common problem in young adults with undefined and prolonged gastrointestinal complaints. Both endoscopic and histological alterations are most prominently found in the duodenum bulb, where LNH or lymphoid follicles are commonly seen. As in coeliac disease, the increase in $\gamma/\delta+$ T-cells is characteristic of cow's milk allergy. However, unlike in coeliac disease, patients with cow's milk allergy do not present antiendomysium antibodies, HLA-DQ2 and -DQ8 genotypes, abnormal HLA-DR expression or duodenal villous changes. Taken together, these results indicate that the mucosal changes are because of a different pathogenetic mechanism in cow's milk allergy than in coeliac disease. Moreover, this histological picture cannot be considered as precursor to coeliac disease, because its striking features are mucosal lymphoid nodules with normal villous architecture.[25]

ILEO-COLONIC LNH

Unlike duodenal LNH, LNH of the mucosa of the lower gastrointestinal tract (i.e. terminal ileum and colon) in children was for several years considered a serendipitous finding without any clinical significance, as an expression of a mucosal response to nonspecific stimuli, most often infection. It was consequently regarded as a pathophysiological phenomenon during infancy and childhood, or, in a lower percentage of cases, as a sign within the spectrum of inflammatory bowel diseases.[26, 27]

More recent studies[3] have shown an elevated frequency of colonic LNH in a large series of consecutive children undergoing colonoscopy for various symptoms (i.e. severe chronic or recurrent abdominal pain and chronic constipation refractory to laxative therapy). Colonic LNH was associated with other endoscopic and/or histological findings pointing to a final diagnosis of IBD in a number of the cases. However, in the vast majority of the patients, who had colonic LNH as the sole endoscopic finding, an appropriate elimination diet followed by food challenge with the offending food(s) led to a diagnosis of FH. Cow's milk was the only causative food protein in the majority of these cases, whereas

multiple hypersensitivity was observed in the remaining patients. In addition, as clinical symptoms reappeared some days after the food challenge, it is clear that most patients had a delayed-type reaction to the offending food(s). The consistency of the association between FH and colonic LNH was confirmed by the fact that a much lower number of patients without colonic LNH had FH. The mean age of patients with isolated LNH and FH was 7.5 years, thus supporting previous studies showing that FH might persist or manifest itself in school-age children and in adults.[25, 28, 29]

In agreement with previous reports on the frequency of colonic LNH in both children and adult patients with haematochezia,[30, 31] gastrointestinal bleeding was present with a significantly higher frequency in the children with isolated colonic LNH and FH than in the whole study groups.

In adults suffering from recurrent rectal bleeding, we demonstrated that LNH not associated to other endoscopic signs was very often caused by multiple food hypersensitivity.[31] In these patients, the clinical history of the allergic patients showed that abdominal pain and bowel habit disturbances very often accompanied the rectal bleeding. It was noteworthy that very often these patients had undergone multiple investigations in the past but without any diagnoses, although the patients themselves often had self-reported a food intolerance, but this was not considered by the clinicians who treated them. It is very probable that the negativity of the IgE-mediated assays in these patients had contributed to a not corrected diagnosis, but it is known that most of the gastrointestinal symptoms caused by food hypersensitivity cannot be correctly diagnosed on the basis of these assays.

Other symptoms associated with endoscopic evidence of isolated colonic LNH were anaemia and growth deficiency, recently recognised as part of the clinical spectrum of FH.[32] Both the humoral and histological findings strongly suggest that colonic LNH is a sensitive endoscopic marker of FH, most likely related to a cell-mediated immune response. In fact, there was a significantly higher number of patients with elevated serum anti-β-lactoglobulin IgG in the colonic LNH group, in accordance with previous reports on FH with gastrointestinal manifestations and with the known allergenicity of β-lactoglobulin, which is the main allergen in cow's milk.[24, 33, 34]

Iacono *et al.*[3] and Turunen *et al.*[35] demonstrated that among children with chronic constipation refractory to laxative therapy some actually have cow's milk hypersensitivity, with characteristic endoscopic and histological findings (i.e. LNH) and elevated densities of γ/δ+ T-cells. This was also strongly supported by the subsidence of constipation or other symptoms during milk elimination and the relapse of original symptoms during the challenge. Ileo-colonic LNH was present in most of the subjects with chronic constipation because of FH and was most prominent in the terminal ileum and transverse colon. In the duodenum bulb, the lesion was also found in many subjects on gastroduodenoscopy. The authors also found an increased density of intraepithelial γ/δ+ T-cells in biopsy samples from the terminal ileum. Therefore, a diagnostic workup in a child with suspected cow's milk-related constipation should include a careful clinical assessment with a milk elimination trial and a long challenge. Endoscopic examinations with biopsies and immunohistochemical studies may help to establish the diagnosis and exclude other conditions.

Finally, Kokkonen *et al.*[36] suggested a strong association between ileo-colonic LNH and FH. In particular, they showed that LNH is a common endoscopic bystander on the mucosa of the lower gastrointestinal tract. Their results supported the view that this is not just a silent finding but is related to enhanced immunological activity, with FH being the most common underlying state, especially in the case of colonic LNH. Indeed, its presence on the mucosa of the colon indicated an association with FH similar to that in the duodenal bulb. If present on the mucosa of the terminal ileum, immune-mediated disorders other than FH (i.e. inflammatory bowel diseases) may also have produced the lesion. Thus, children diagnosed with LNH of the lower gastrointestinal tract (especially of the colon) should be carefully assessed for the possibility of hypersensitivity to basic foodstuffs by whatever techniques are appropriate, including oral challenge. In addition, according to the above study,[35] most of the patients with LNH related to FH showed similar lesions on the mucosa of the duodenum. Of note, the coexistence of LNH in these two locations could not be demonstrated in all patients, confirming the view that FH in children may produce patchy or diffuse LNH in any part of the gastrointestinal tract. LNH of the colon was even seen in children diagnosed for FH being treated with an elimination diet, which supports the view that the increase in lymphoid tissue persists even after the triggering foodstuffs have been eliminated. The same was found in the duodenum.

Tables 1 and 2 summarised the study regarding LNH and FH. Figure 1 shows a typical picture of colonic LNH in a patient suffering from FH, diagnosed at the 'Di Cristina' Pediatric Hospital of Palermo.

Table 1 | Lymphoid nodular hyperplasia (LNH) in food hypersensitivity (FH) patients

Text reference	Authors	Clinical presentation	Cases number	Age (years range)	Cases number and % of patients affected with FH	Cases number and % of patients affected with LNH
11	Kokkonen J	Recurrent abdominal pain	84	1.6–15	28/84 (33%)	9/28 (32%)
19	Kokkonen J	Recurrent abdominal pain or growth retardation	Untreated FH: 22 Treated FH: 14 Recurrent abdominal pain without FH: 44 Healthy controls: 54 Total: 134	3–15	Untreated FH: 22/22 (100%) Treated FH: 14/14 (100%)	Untreated FH: 11/22 (50%) Treated FH: 5/14 (36%) Total FH: 21/36 (58%) Recurrent abdominal pain: 6/44 (14%) Total: 27/134 (34%)
20	Kokkonen J	Recurrent abdominal pain and diarrhoea	Cow's milk FH: 15 Suspected cow's milk FH: 12 Coeliac disease: 11 Controls: 12 Total: 50	Cow's milk FH: 6–4 Suspected cow's milk FH: 7–14 Coeliac disease: 8–15 Controls: 6–15	Cow's milk FH: 15/15 (100%) Suspected cow's milk FH: 12/12 (100%)	Cow's milk FH: 9/15 (60%) Suspected cow's milk FH: 8/12 (67%) Coeliac disease: 1/11 (9%) Controls: 2/12 (17%) Total: 20/50 (40%)
31	Turunen S	Constipation	35	3–15	12/35 (34%)	8/12 (67%)
33	Kokkonen J	Recurrent gastrointestinal symptoms and/or growth retardation	102	1–15	Diagnosed FH: 36/102 (35%) Suspected FH: 24/102 (24%)	18/36 with diagnosed FH (50%) 8/24 with suspected FH (33%)
34	Kokkonen J	Gastrointestinal symptoms	Untreated FH: 20 Treated FH: 17 Coeliac Disease: 12 Controls: 12 Total: 61	2–15	Untreated FH: 20 (33%) Treated FH: 17 (28%)	Untreated FH: 14/20 (70%) Treated FH: 8/17 (47%) Coeliac Disease: 0 Controls: 0 Total: 22/61 (36%)

Aliment Pharmacol Ther 2012; 35: 1000-1009

Table 2 | Food hypersensitivity (FH) in lymphoid nodular hyperplasia (LNH) patients

Text reference	Authors	Clinical presentation	Cases number	Age (years range)	Cases number and % of patients affected with LNH	Cases number and % of patients affected with FH
10	Kokkonen J	Recurrent abdominal pain	63	1.9–15	12/63 (19%)	9/12 (75%)
23	Iacono G	Severe chronic or recurrent abdominal pain, constipation, diarrhoea, bloody diarrhoea, growth retardation, chronic vomiting	245	3–10	Total: 73/245 (30%) Isolated LNH without IBD: 52/245 (21.2%)	Total FH: 103/245 (42%) FH with isolated LNH without IBD: 43/52 (83%)
27	Carroccio A	Rectal bleeding	64	18–79	10/64 (16%)	9/10 with LNH (90%)
32	Kokkonen J	Chronic colitis, IBD, systemic vasculitis	140	3–16	Colonic LNH: 46/140 (33%) 36 without colitis (26%) 9 with colitis (6%) 2 with Crohn (0.7%) Ileocolonic LNH: 50/74 (67%) 35 without colitis (47%); 13 with colitis (17%); 2 with Crohn (3%). Duodenal bulb LNH: 22/102 (22%)	Colonic LNH: 25/46 (54%) Ileocolonic LNH: 18/50 (36%) Duodenal bulb LNH: 13/22 (59%)

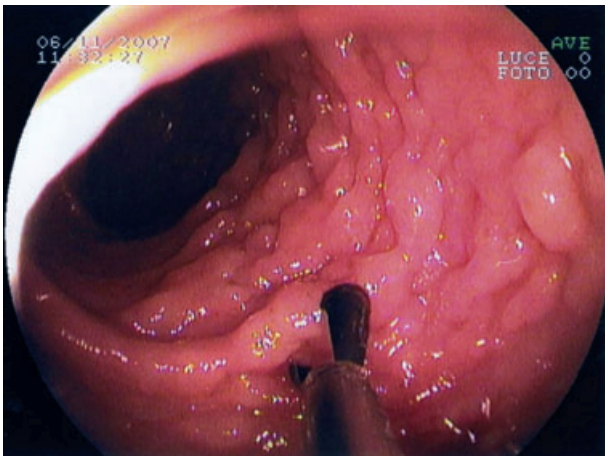

Figure 1 | Typical picture of colonic lymphoid nodular hyperplasia in a patient suffering from food hypersensitivity.

LNH AND DENSITY OF $\gamma/\delta+$ T-CELLS

An increase in the density of $\gamma/\delta+$ T-cell receptor-bearing intraepithelial lymphocytes is considered to be specific to gluten-sensitive enteropathy, although it must be recognised that the real role of $\gamma/\delta+$ T-cells in this disease is still enigmatic (i.e. they may remain elevated even on a gluten-free diet or decrease on elimination diet). In addition, their normal density has not yet been precisely determined.[37, 38] The connection between intraepithelial $\gamma/\delta+$ T-cells and other members of innate immunity are highlighted by the results of Kokkonen *et al.*, who recently demonstrated in coeliac disease and in cow's milk-sensitive enteropathy that serum CD23, a protein expressed in the lymphoid follicles, tends to increase. In coeliac disease, serum CD23 levels may provide information about the severity of villous atrophy, whereas in cow's milk-sensitive enteropathy high serum FasL, functionally connected with IL-15 proliferation and apoptosis of the intraepithelial lymphocytes, indicates an increase in intraepithelial lymphocytes and the presence of LNH, suggesting the importance of FasL-mediated mechanisms in the pathogenesis of these cow's milk-sensitive enteropathy features.[39]

However, in children with FH and LNH of the duodenum bulb it is possible to demonstrate a higher than normal density of $\gamma/\delta+$ intraepithelial lymphocytes, together with a higher density of IFN-γ positive cells in the lamina propria and a higher proportion of crypt cells in mitosis, as well as a rise in intraepithelial $\gamma/\delta+$ T-cells in untreated FH, whereas patients on an elimination diet at the time of the examination show low counts. Thus, $\gamma/\delta+$ T-cells, which are considered to be markers of FH,

seem to react more rapidly during dietary therapy and only increase in active and untreated cases. LNH could represent a more long-standing or even permanent up-regulation of immunological response to food antigens, persisting even after the deleterious antigen has been removed from the diet.[40–42] In this context, parental assessments of a likely FH agreed with these mucosal findings (increased intraepithelial T-cells and $\gamma/\delta+$ cells) in a significant number of cases, even when food challenges were reportedly negative. In fact, food challenges could be negative in FH patients, especially those with non-IgE-mediated FH mechanisms.[40]

As regards to LNH of the terminal ileum, some authors have demonstrated that this pathology is associated with increased densities of $\gamma/\delta+$ T-cells, as in children with LNH of the duodenal bulb and untreated FH. Surprisingly, they found not only this association but also a close association between an increase in these cells and right-sided colitis and pancolitis. In contrast, neither Crohn's disease nor typical left-sided ulcerous colitis showed any association. Thus, it would be possible to classify colitis in children into $\gamma/\delta+$ or 'allergic' and $\gamma/\delta-$ or 'non-allergic diseases'. The former seems to be an entity starting from the terminal ileum as lymphoid hyperplasia and continuing into the caecum as chronic colitis, extending in a few cases as far as the rectum. Clinically, this disease resembles what is traditionally classified as 'indeterminate colitis'. The other form of colitis seems to start locally on the left side, probably on the rectal mucosa, and extends proximally. Clinically, this entity is compatible with typical ulcerous colitis. A differential diagnosis might be made by simply counting the density of $\gamma/\delta+$ T-cells on the terminal ileum mucosa. Thus, it seems evident that in Crohn's disease and left-sided colitis, different cytokine cascades and pathogenetic mechanisms to those involved in right-sided colitis become activated.[43] These results are in accordance with a number of previous studies suggesting that Crohn's disease with granulomas is a T_H1- and/or T_H17-mediated disease.[44–46]

At present, no immunohistochemical studies on colonic biopsies are available of patients with colonic LNH, either related or unrelated to FH.

Finally, the mechanisms by which the enhanced local immune responses (i.e. LNH and $\gamma/\delta+$ intraepithelial T-cells) cause gastrointestinal symptoms remain mostly obscure. FH symptoms have been suggested as being due to a cytokine imbalance. Children with delayed-type cow's milk allergy showed lower IL-2 and IL-18 mRNA expression in the duodenum and higher CCR-4 and IL-6 mRNA expression in the terminal ileum, compared with controls and children with coeliac disease. The mRNA expression levels of regulatory cytokines (i.e. transforming growth factor-beta and IL-10) remained similar in patients and controls. Children with delayed-type gastrointestinal cow's milk allergy showed a unique pattern of local intestinal hypersensitivity with TH2 response-related characteristics, a profile clearly differing from those with coeliac disease.[47, 48]

LNH AND AUTISTIC DISORDERS

The autistic spectrum disorder, or ASD, is a neurodevelopmental disorder characterised by socially aloof behaviour and impairment of language and social interaction. Gastrointestinal symptoms are described in 9–54% of autistic children, the most common of which are constipation, diarrhoea and abdominal distension. The gastrointestinal abnormalities reported in autism include adverse reaction to foods (i.e. non-IgE-mediated FH), inflammation (oesophagitis, gastritis, duodenitis, enterocolitis), increased intestinal permeability, low activities of disaccharidase enzymes, dysbiosis with bacterial overgrowth, impairment of detoxification (i.e. defective sulfation of ingested phenolic amines) and exorphin intoxication (by opioids, i.e. caseomorphine and gluteomorphine derived from casein and gluten). A beneficial effect of dietary intervention on the behaviour and cognition of some autistic children indicates a functional relationship between the alimentary tract and the central nervous system.[49–51] However, this is a strongly controversial issue and data contrasting with the above findings have been published.[52, 53]

In addition to the above-mentioned gastrointestinal abnormalities, some authors also demonstrated that several ileo-colonic LNH in children with ASD, referred to a gastroenterology clinic for chronic gastrointestinal symptoms, warranted investigation by ileo-colonoscopy.[54–56] The findings were compared with control groups of children who were developmentally normal. Children with ASD are less likely to present with abdominal pain and more likely to present with constipation. However, this could reflect the relative inability of children with autism to communicate the experience of pain. The autistic children showed a higher frequency of LNH in the terminal ileum (93% vs. 14.3%) and the colon (30% vs. 3%).

If the data on gastrointestinal manifestations in autistic children continue to mount, then the basis for a link will need to be thoroughly investigated to ascertain whether the intestinal and cognitive

manifestations are merely different components of a complex syndrome of unknown pathogenesis, or could be causally related.

It is possible to hypothesise a primitive, poorly understood immune dysfunction that predisposes autistic children to a broad spectrum of immunologically based disorders, i.e. eczema, upper respiratory tract infections, FH, as well as ileo-colonic LNH. The impaired cognitive function could then be explained on the basis of an 'entero-colonic encephalopathy', analogous to hepatic encephalopathy. Specifically, the intestinal lesion results in an increased intestinal permeability to exogenous peptides of dietary origin, ultimately leading to the disruption of neuroregulatory mechanisms and normal brain development. These possibilities should be investigated further.[49, 50, 57]

Table 3 | Lymphoid nodular hyperplasia: aetiologies and diagnostic procedures

Aetiologies	Diagnostic procedures
IgA deficiency	Laboratory measurement of IgA level in the blood
Common variable immunodeficiency	Low serum IgG concentration Reduced serum concentrations of other immunoglobulins, i.e. IgA or IgM Low CD4+ count, associated with a normal to increased CD8+ count *In vitro* proliferative responses of peripheral blood lymphocytes Deficient cytokine production by peripheral blood lymphocytes Evidence of noncaseating granulomas on imaging studies or biopsy
Food hypersensitivity	Prick tests Radioallergosorbent test (RAST) Elimination diet and oral food challenge
Human immunodeficiency virus (HIV) infection	HIV enzyme-linked immunosorbent assay (ELISA) HIV Western blot test
Human T-cell lymphotropic viruses (HTLV)-I & II infection	HTLV ELISA HTLV Western blot test Detection of proviral DNA by Polymerase Chain Reaction (PCR) Quantitative PCR assay
Cytomegalovirus (CMV) infection	Serological assays, i.e. CMV IgM and IgG antibodies by ELISA and Radio Immune Assay (RIA) CMV IgG avidity
Epstein-Barr Virus (EBV) Infection	Serological assays for viral capsid antigen (IgG and IgM), early antigen (IgG) and EBV nuclear antigen (IgG) antibodies
Yersinia enterocolitica infection	Recovery of *Yersinia* from stool samples, blood and lymph nodes Culture in Cefsulodin-Irgasan-Novobiocin (CIN) or MacConkey agar Serodiagnosis by tube agglutination, ELISA and RIA PCR, DNA microarray and immunohistochemical staining to detect *Y. enterocolitica* DNA
Helicobacter pylori infection	ELISA detection of *H. pylori* specific antibodies, IgG and IgM Breath tests (i.e. urea breath tests) Stool tests (detection of *H. pylori* proteins by ELISA)
Giardiasis	Stool ova and parasites detection *Giardia* stool antigen test
Juvenile idiopathic arthritis (JIA)	History Physical examination findings Laboratory studies help to exclude underlying disorders, classify type of arthritis and evaluate for extra-articular manifestations Imaging of affected joints is usually indicated
Other connective diseases	History Physical examination findings Non-organ-specific autoantibodies Laboratory assays and imaging techniques to detect e type organ injury
Intestinal lymphoma	Endoscopy and biopsy Wireless video capsule camera Abdominal computerised tomography (CT) with intravenous contrast Arteriography of the intestinal arteries (in case of tumour bleeding) Exploratory surgery

CONCLUSION: A DIAGNOSTIC WORK-UP FOR LNH RELATED TO FH

In the presence of LNH, demonstrated during upper and/or lower endoscopy performed for severe gastrointestinal symptoms, the possible aetiologies and the related diagnostic procedures are shown in Table 3, where we considered FH together with many other diseases. For diagnostic purposes, the presence of lymphoid follicles in the biopsy specimen and a rise in $\gamma/\delta+$ T-cells alone would not be sufficient in patients with suspected FH showing endoscopic picture of LNH of the duodenal bulb and/or of the terminal ileum and the colon. The diagnostic problem is the patchy nature of all these signs, as they can be dispersed at any one site along the gastrointestinal tract from the oral cavity to the anus. In addition, there is a significant lack of serological markers for a diagnostic assessment of mucosal abnormality. At present, when clinically assessing FH, we rely on a clinical evaluation, including a lengthy elimination diet and challenge tests, together with endoscopic and/or immunohistochemical findings as a sign of enhanced immune activity.

Considering the possible co-existence of duodenal and ileo-colonic LNH, upper endoscopy can also be recommended in children with suspected FH and ileo-colonic LNH, especially in those presenting with additional upper abdominal symptoms (i.e. vomiting and dyspepsia). Likewise, lower endoscopy might be additionally performed in patients with suspected FH and endoscopically diagnosed LNH of the duodenal bulb also presenting with lower abdominal symptoms (i.e. severe chronic or recurrent abdominal pain, or chronic constipation refractory to laxative therapy or presence of blood in stools).[40]

ACKNOWLEDGEMENT

Declaration of personal and funding interests: None.

REFERENCES

1. Kuper CF. Histopathology of mucosa-associated lymphoid tissue. *Toxicol Pathol* 2006; **34**: 609–15.
2. Kunisawa J, Fukuyama S, Kiyono H. Mucosa-associated lymphoid tissues in the aerodigestive tract: their shared and divergent traits and their importance to the orchestration of the mucosal immune system. *Curr Mol Med* 2005; **5**: 557–72.
3. Iacono G, Ravelli A, Di Prima L, *et al.* Colonic lymphoid nodular hyperplasia in children: relationship to food hypersensitivity. *Clin Gastroenterol Hepatol* 2007; **5**: 361–6.
4. Ng SC, Kamm MA, Stagg AJ, Knight SC. Intestinal dendritic cells: their role in bacterial recognition, lymphocyte homing, and intestinal inflammation. *Inflamm Bowel Dis* 2010; **16**: 1787–807.
5. Venter C, Arshad SH. Epidemiology of food allergy. *Pediatr Clin North Am* 2011; **58**: 327–49.
6. Saffouri B, Mishriki Y, Bartolomeo RS, Fuchs B. The value of endoscopy in the diagnosis of lymphoid nodular hyperplasia. *J Clin Gastroenterol* 1980; **2**: 169–71.
7. Khuroo MS, Khuroo NS, Khuroo MS. Diffuse duodenal nodular lymphoid hyperplasia: a large cohort of patients etiologically related to Helicobacter pylori infection. *BMC Gastroenterol* 2011; **11**: 36.
8. Vestergaard H, Westergaard T, Wohlfahrt J, Pipper C, Melbye M. Association between intussusception and tonsil disease in childhood. *Epidemiology* 2008; **19**: 71–4.
9. Coulibaly B, Piercecchi-Marti MD, Bartoli C, Liprandi A, Sanvoisin A, Leonetti G. Benign lymphoid polyposis: two diffuse cases leading to fatal intestinal ischemia in children. *Pediatr Int* 2009; **51**: 428–31.
10. Boyce JA, Assa'ad A, Burks AW, *et al.* Guidelines for the Diagnosis and Management of Food Allergy in the United States: Summary of the NIAID-Sponsored Expert Panel Report. *J Allergy Clin Immunol* 2010; **126**: 1105–18.
11. Sicherer SH, Sampson HA. Food allergy. *J Allergy Clin Immunol* 2010; **125**(Suppl. 2): S116–25.
12. Lack G. Clinical practice. Food allergy. *N Engl J Med* 2008; **359**: 1252–60.
13. Story RE. Manifestations of food allergy in infants and children. *Pediatr Ann* 2008; **37**: 530–5.
14. Berni Canani R, Ruotolo S, Discepolo V, Troncone R. The diagnosis of food allergy in children. *Curr Opin Pediatr* 2008; **20**: 584–9.
15. Kokkonen J, Karttunen TJ, Niinimäki A. Lymphonodular hyperplasia as a sign of food allergy in children. *J Pediatr Gastroenterol Nutr* 1999; **29**: 57–62.
16. Kokkonen J, Ruuska T, Karttunen TJ, Niinimäki A. Mucosal pathology of the foregut associated with food allergy and recurrent abdominal pains in children. *Acta Paediatr* 2001; **90**: 16–21.
17. Van den Brande P, Geboes K, Vantrappen G, *et al.* Intestinal nodular lymphoid hyperplasia in patients with common variable immunodeficiency: local accumulation of B and CD8(+) lymphocytes. *J Clin Immunol* 1988; **8**: 296–306.
18. Sauerbrei E, Castelli M. Hypogammaglobulinemia and nodular lymphoid hyperplasia of the gut. *J Can Assoc Radiol* 1979; **30**: 62–3.
19. Sánchez Rodríguez A, Martínez JM, de Letona L, *et al.* Nodular lymphoid hyperplasia of the small bowel with IgA deficiency and hemolytic anemia. *Med Clin* 1980; **75**: 261–5.
20. Levendoglu H, Rosen Y. Nodular lymphoid hyperplasia of gut in HIV infection. *Am J Gastroenterol* 1992; **87**: 1200–2.
21. Ward H, Jalan KN, Maitra TK, Agarwal SK, Mahalanabis D. Small intestinal nodular lymphoid hyperplasia in patients with giardiasis and normal serum immunoglobulins. *Gut* 1983; **24**: 120–6.
22. Kokkonen J, Arvonen M, Vähäsalo P, Karttunen TJ. Intestinal immune activation in juvenile idiopathic arthritis and connective tissue disease. *Scand J Rheumatol* 2007; **36**: 386–9.
23. Matuchansky C, Morichau-Beauchant M, Touchard G, *et al.* Nodular lymphoid hyperplasia of the small bowel associated with primary jejunal malignant lymphoma. Evidence

favoring a cytogenetic relationship. *Gastroenterology* 1980; **78**: 1587–92.
24. Kokkonen J, Tikkanen S, Karttunen TJ, Savilahti E. A similar high level of immunoglobulin A and immunoglobulin G class milk antibodies and increment of local lymphoid tissue on the duodenal mucosa in subjects with cow's milk allergy and recurrent abdominal pains. *Pediatr Allergy Immuno* 2002; **13**: 129–36.
25. Kokkonen J, Haapalahti M, Laurila K, Karttunen TJ, Mäki M. Cow's milk protein-sensitive enteropathy at school age. *J Pediatr* 2001; **139**: 797–803.
26. Canto J, Arista J, Hernández J. Nodular lymphoid hyperplasia of the intestine. Clinico-pathologic characteristics in 11 cases. *Rev Invest Clin* 1990; **42**: 198–203.
27. Gerson CD, Marshak RH, Lindner AE. The radiology corner. Nodular lymphoid hyperplasia of the small intestine. *Am J Gastroenterol* 1974; **62**: 371–6.
28. Iacono G, Cavataio F, Montalto G, Soresi M, Notarbartolo A, Carroccio A. Persistent cow's milk protein intolerance in infants: the changing faces of the same disease. *Clin Exp Allergy* 1998; **28**: 817–23.
29. Carroccio A, Di Prima L, Iacono G, *et al.* Multiple food hypersensitivity as a cause of refractory chronic constipation in adults. *Scand J Gastroenterol* 2006; **41**: 498–504.
30. Kaplan B, Benson J, Rothstein F, Dahms B, Halpin T. Lymphonodular hyperplasia of the colon as a pathologic finding in children with lower gastrointestinal bleeding. *J Pediatr Gastroenterol Nutr* 1984; **3**: 704–8.
31. Carroccio A, Iacono G, Di Prima L, *et al.* Food hypersensitivity as a cause of rectal bleeding in adults. *Clin Gastroenterol Hepatol* 2009; **7**: 120–2.
32. Somers L. Food allergy: nutritional considerations for primary care providers. *Pediatr Ann* 2008; **37**: 559–68.
33. Iacono G, Carroccio A, Cavataio F, *et al.* Gastroesophageal reflux and cow's milk allergy in infants: a prospective study. *J Allergy Clin Immunol* 1996; **97**: 822–7.
34. Carroccio A, Scalici C, Di Prima L, Iacono G. IgG anti-betalactoglobulin in children with IBS symptoms: a valid aid to decide for the elimination diet (e-letters). *Gut* 2005; **53**: 1459–64.
35. Turunen S, Karttunen TJ, Kokkonen J. Lymphoid nodular hyperplasia and cow's milk hypersensitivity in children with chronic constipation. *J Pediatr* 2004; **145**: 606–11.
36. Kokkonen J, Karttunen TJ. Lymphonodular hyperplasia on the mucosa of the lower gastrointestinal tract in children: an indication of enhanced immune response? *J Pediatr Gastroenterol Nutr* 2002; **34**: 42–6.
37. Savilahti E, Arato A, Verkasalo M. Intestinal gamma/delta receptor-bearing T lymphocytes in celiac disease and inflammatory bowel diseases in children. Constant increase in celiac disease. *Pediatr Res* 1990; **28**: 579–81.
38. Järvinen TT, Kaukinen K, Laurila K, *et al.* Intraepithelial lymphocytes in celiac disease. *Am J Gastroenterol* 2003; **98**: 1332–7.
39. Kokkonen TS, Augustin MT, Kokkonen J, Karttunen R, Karttunen TJ. Serum and tissue CD23, IL-15 and Fas-L in cow's milk protein-sensitive enteropathy and in coeliac disease. *J Pediatr Gastroenterol Nutr* 2011 [Epub ahead of print].
40. Kokkonen J, Holm K, Karttunen TJ, Mäki M. Enhanced local immune response in children with prolonged gastrointestinal symptoms. *Acta Paediatr* 2004; **93**: 1601–7.
41. Kokkonen J, Holm K, Karttunen TJ, Mäki M. Children with untreated food allergy express a relative increment in the density of duodenal gammadelta+ T cells. *Scand J Gastroenterol* 2000; **35**: 1137–42.
42. Veres G, Westerholm-Ormio M, Kokkonen J, Arato A, Savilahti E. Cytokines and adhesion molecules in duodenal mucosa of children with delayed-type food allergy. *J Pediatr Gastroenterol Nutr* 2003; **37**: 27–34.
43. Kokkonen J, Ruuska T, Karttunen TJ, Mäki M. Lymphonodular hyperplasia of the terminal ileum associated with colitis shows an increase gammadelta+ t-cell density in children. *Am J Gastroenterol* 2002; **97**: 667–72.
44. Peluso I, Pallone F, Monteleone G. Interleukin-12 and Th1 immune response in Crohn's disease: pathogenetic relevance and therapeutic implication. *World J Gastroenterol* 2006; **12**: 5606–10.
45. Bamias G, Sugawara K, Pagnini C, Cominelli F. The Th1 immune pathway as a therapeutic target in Crohn's disease. *Curr Opin Investig Drugs* 2003; **4**: 1279–86.
46. Brand S. Crohn's disease: Th1, Th17 or both? The change of a paradigm: new immunological and genetic insights implicate Th17 cells in the pathogenesis of Crohn's disease. *Gut* 2009; **58**: 1152–67.
47. Hauer AC, Breese EJ, Walker-Smith JA, MacDonald TT. The frequency of cells secreting interferon-gamma and interleukin-4, -5, and -10 in the blood and duodenal mucosa of children with cow's milk hypersensitivity. *Pediatr Res* 1997; **42**: 629–38.
48. Paajanen L, Kokkonen J, Karttunen TJ, Tuure T, Korpela R, Vaarala O. Intestinal cytokine mRNA expression in delayed-type cow's milk allergy. *J Pediatr Gastroenterol Nutr* 2006; **43**: 470–6.
49. Erickson CA, Stigler KA, Corkins MR, Posey DJ, Fitzgerald JF, McDougle CJ. Gastrointestinal factors in autistic disorder: a critical review. *J Autism Dev Disord* 2005; **35**: 713–27.
50. Goldberg EA. The link between gastroenterology and autism. *Gastroenterol Nurs* 2004; **27**: 16–9.
51. White JF. Intestinal pathophysiology in autism. *Exp Biol Med* 2003; **228**: 639–49.
52. Black C, Kaye JA, Jick H. Relation of childhood gastrointestinal disorders to autism: nested case–control study using data from the UK General Practice Research Database. *BMJ* 2002; **325**: 419–421.
53. Buie T, Campbell DB, Fuchs GJ 3rd, *et al.* Evaluation, diagnosis, and treatment of gastrointestinal disorders in individuals with ASDs: a consensus report. *Pediatrics* 2010; **125**(Suppl 1): S1–18.
54. Wakefield AJ, Ashwood P, Limb K, Anthony A. The significance of ileocolonic lymphoid nodular hyperplasia in children with autistic spectrum disorder. *Eur J Gastroenterol Hepatol* 2005; **17**: 827–836.
55. MacDonald TT. The significance of ileocolonic lymphoid nodular hyperplasia in children with autistic spectrum disorder. *Eur J Gastroenterol Hepatol* 2006; **18**: 569–71.
56. Jass JR. The intestinal lesion of autistic spectrum disorder. *Eur J Gastroenterol Hepatol* 2005; **1**: 821–2.
57. Jyonouchi H. Food allergy and autism spectrum disorders: is there a link? *Curr Allergy Asthma Rep* 2009; **9**: 194–201.