Ileocolonic Lymphonodular Hyperplasia in Children Related to Etiologies Ranging from Food Hypersensitivity to Familial Mediterranean Fever

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Abstract

Objective: We aimed to share our observations on the demographics, clinical characteristics, and outcomes of lymphonodular hyperplasia (LNH) in children. Subjects and Methods: The study included children on whom colonoscopy was performed between January 2015 and May 2018 (n = 361). Demographics, treatment modalities, and outcomes of the patients with LNH were recorded. Results: LNH was found in 66 patients (18.3%; mean age 8.6 ± 5.96 years, 59.1% male). We found that the etiologic factors were food hypersensitivity (FH) in 25 (37.8%), nonspecific colitis in 12 (18.2%), irritable bowel syndrome in 10 (15.2%), familial Mediterranean fever in 7 (10.6%), primary immunodeficiency in 4 (6.1%), and intestinal dysmotility, oxyuriasis, Crohn’s disease, and giardiasis in 1 (1.5%) patient. Additionally, in the genetic analysis of patients with idiopathic LNH (n = 4), we detected heterozygote MEFV mutations in all. Cow’s milk and egg (25%) were the most common allergens in patients with FH. Symptoms of all patients (n = 25) improved after an elimination diet. Conclusions: LNH is a common finding in pediatric colonoscopies with a variety of etiologies ranging from FH and familial Mediterranean fever to immunodeficiency.
terminal ileum and appendix, and the colon also contains a considerable number of lymphoid aggregates. They are evident as large numbers (> 10) of lymphoid nodules with a diameter of 2–10 mm and a flat and yellow-white appearance during colonoscopy that defines them as lymphonodular hyperplasia (LNH). Histopathologic examination reveals hyperplastic lymphoid follicles and mitotically active germinal centers with lymphocytic mantles [1, 2].

LNH is a common finding during pediatric colonoscopy, but its clinical significance and etiologic factors are unclear. Previous studies have defined the association of LNH with food allergy, infections, and immunodeficiency syndromes in adults [3–6]. Additionally, it has been shown to have an association with connective tissue diseases, inflammatory bowel disease (IBD), juvenile idiopathic arthritis, lymphoma, and refractory constipation [3]. Interestingly, an association was shown between LNH and autism due to chronic constipation [7]. It can also be seen in normal individuals without any symptoms or may be related to nonspecific chronic abdominal symptoms [3, 8, 9].

Here, we describe the demographic and clinical characteristics and outcomes of LNH in pediatric patients.

### Subjects and Methods

This is a retrospective study for which data were obtained from hospital files. It included all patients (<18 years of age) who had undergone full colonoscopy including ileal intubation between January 2015 and May 2018 in a pediatric gastroenterology unit of a tertiary hospital. The demographic characteristics, symptoms, laboratory, endoscopic and histopathologic findings, treatment modalities, and outcomes of the patients with LNH were recorded. All colonoscopic procedures were performed on a Pentax EPK-100 device (HOYA Corp., Tokyo, Japan) by M.C. and E.S. Diagnosis of LNH was based on the presence of an endoscopic appearance and/or histopathologic findings of LNH. LNH was defined as: (i) >10 lymphoid nodules with a diameter >2 mm on colonoscopic examination, and (ii) hyperplastic lymphoid follicles and mitotically active germinal centers with lymphocytic mantles on histopathologic examination [5, 10]. All colonoscopic procedures were performed on a Pentax device (HOYA Corp.). Biopsies of abnormal lesions were obtained in all sections of the colon (in the rectum and sigmoid, descending, transverse, and ascending colon) and terminal ileum even when these appeared normal.

Depending on the individual clinical and laboratory data, a diagnostic workup was done including complete blood count, complete biochemical tests, stool microscopy, immunologic tests, and possible infectious etiologies (stool culture for bacteria, viruses, and parasites; serum PCR for EBV, CMV, and HIV). Skin prick tests and/or food-specific immunoglobulin E (IgE) tests were also performed. Patients with positive results, except for patients <1 year old, were put on an elimination diet elimination
Ileocolonic LNH in Children

According to the test findings, younger patients underwent a therapeutic 2-food diet challenge (cow’s milk and egg) with formula or breast milk regardless of the test findings. A positive clinical response was accepted as food hypersensitivity (FH). According to previous studies, LNH is a common manifestation of familial Mediterranean fever (FMF) [11]. Therefore, we evaluated the patients with idiopathic LNH for FMF via clinical and/or genetic analysis. A final diagnosis of FMF was made, according to the Tel Hashomer criteria [12], by a pediatric rheumatologist. The diagnosis of irritable bowel syndrome (IBS) was made by clinical parameters as defined previously [13]. Skin prick test and/or food-specific IgE were negative in patients with IBS. Nonspecific colitis was defined as an increase in chronic inflammatory cells without architectural abnormalities, the presence of multiple basal lymphoid aggregates or basal inflammatory cells immediately above the muscularis mucosae, and no reactive changes on the surface epithelium or in the crypts [14]. The diagnosis of other conditions such as IBD (including Crohn’s disease, ulcerative colitis, and indeterminate colitis), infectious colitis, and microscopic colitis were excluded before a diagnosis of nonspecific colitis was made. Skin prick test and/or food-specific IgE were negative in these patients.

All calculations in our study were performed using the Statistical Package for Social Sciences v23 (IBM Corp., Armonk, NY, USA), and the continuous variables were expressed as mean ± standard deviation and categorical variables as n (%).

**Results**

A total of 401 colonoscopies were performed on 361 patients during the study period. LNH was found in 66 patients (18.3%, 95% CI 14.3–22.9) (Fig. 1, 2). Demographic features and indications for the colonoscopy are shown in Table 1. LNH was detected in the terminal ileum in 40 patients (60.6%), in the colon in 19 (28.8%), and in both the ileum and colon in 7 (10.6%). Additional to LNH, ileal aphthous ulcers in 2 patients (3%) and colonic ulcers in 2 patients (3%) were detected.

After all examinations, we found that the etiologic factors in LNH were FH in 25 (37.8%), nonspecific colitis in 12 patients (18.2%), IBS in 10 (15.2%, constipation-dominant in 5 and diarrhea-dominant in 5), FMF in 7 (10.6%), and primary immunodeficiency in 4 (6.1%). Intestinal dysmotility, oxyuriasis, and giardiasis were detected in 1 patient (1.5%). Five of the seven patients with FMF were receiving colchicine treatment and had chronic gastrointestinal system symptoms (FMF-related LNH). After the colonoscopy, 2 patients with LNH were diagnosed as having FMF by clinical and/or genetic analysis (primary FMF-related LNH). Additionally, in the genetic analysis of patients with idiopathic LNH (n = 4, 6.1%), we detected heterozygote MEFV mutations (2 of G304P and 1 of

**Fig. 1.** Lymphonomodular hyperplasia of the terminal ileum (a) and colon (b).

**Fig. 2.** Terminal ileum biopsy: hyperplasic lymphoid follicles, suggesting nodular lymphoid hyperplasia. HE. ×1,000.
E148Q and L110P) in 4 patients. But they did not have any clinical findings compatible with FMF during the follow-up. The demographic features and etiology of patients with LNH are shown in Table 2.

There were 25 patients with suspected FH. Twelve of these were treated with an elimination diet according to positive skin prick test and/or food-specific IgE findings. In total, 16 allergens were positive, and 4 patients had multiple food allergies. Cow’s milk and egg (25%) were the most common allergens (Fig. 3). Additionally, aeroal-

### Table 2. Demographic features and etiology of patients with LNH (n = 66)

| Etiology                                      | n  | (%)  |
|----------------------------------------------|----|------|
| Food hypersensitivity                        | 25 | (37.8) |
| Nonspecific colitis                          | 12 | (18.2) |
| IBS (constipation/diarrhea dominant)         | 10 | (15.2) (5/5) |
| FMF (FMF-related LNH/primary FMF-related LNH) | 7  | (10.6) (5/2) |
| CVID                                         | 4  | (6.1) |
| Dysmotility (operated HD)                    | 1  | (1.5) |
| Giardiasis                                   | 1  | (1.5) |
| Oxyuriasis                                   | 1  | (1.5) |
| Crohn’s disease                              | 1  | (1.5) |
| Idiopathic LNH (heterozygous MEFV mutation)  | 4  | (6.1) |

Values express n (%), unless otherwise indicated. CVID, common variable immune deficiency; FMF, familial Mediterranean fever; IBS, irritable bowel syndrome; HD, Hirschsprung disease.

a Mean ± SD.

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### Figure 3. Distribution of food allergens.

1. **Cow’s milk** (n = 4, 25%)
2. **Egg** (n = 4, 25%)
3. **Soy** (n = 2, 12.5%)
4. **Peanut** (n = 1, 6%)
5. **Wheat** (n = 2, 12.5%)
6. **Hazelnut** (n = 3, 19%)

The final diagnosis of patients with ileal aphthous ulcers were Crohn’s disease and food allergy; patients with colonic ulcers had FMF-related LNH and CVID. Patients with idiopathic LNH and heterozygous MEFV mutation were monitored in outpatient clinics without any treatment.
Discussion

In this study, we present the demographic and clinical findings, etiologies, and outcomes of children with LNH. We found that: (i) it is a common finding in pediatric colonoscopies (18.3%), (ii) the majority of LNH cases are associated with FH (37.8%), (iii) in addition to FH and IBS (15.2%), immunodeficiency (6.1%), IBD (1.5%), FMF (7.6%), and carrying MEFV mutations (6.1%) may be associated with ileocolonic LNH, and (iv) most of the patients improved after the underlying condition was treated.

Luminal commensals and pathogenic flora induce the production of specific IgA antibodies within Peyer’s patches and lymphoid follicles. In this response, lymphoid cells accumulate and induce the evolution of M cells in the surface epithelium. Secreted IgA is induced by the stimulation of luminal factors such as chronic inflammation, infections, or protein antigens. An imbalance or dysfunction in the secretion of luminal IgA has been suggested to cause LNH [15]. LNH in association with immunodeficiency might be explained as a compensatory mechanism. Similarly, an increase in the number of lymphoid follicles in the colon of patients with colitis (non-specific, IBD, or infectious) may represent similar attempts to control the inflammation by increased production of IgA. Mechanisms linking food allergy to LNH are not clear. An association of a history of non-IgE-mediated food allergy in infancy and an increase in antiallergen IgA levels has been shown. Additionally, deficient T-helper 1 function has been reported in the peripheral blood of patients with LNH (similar to in patients with delayed-type food allergy), such as increased interleukin (IL)–6 messenger RNA (mRNA) and interferon (IFN)-γ mRNA in the colonic mucosa and increased IFN-γ, IL-4, and IL-10 secretion in the periphery [16]. Diet-related changes in the microbiome (in IBD) and longer exposure to mucosal content (in dysmotility syndromes) may also induce unbalanced IgA secretion [15].

LNH is a common finding during pediatric colonoscopies. Gurkan et al. [11] reported that LNH was found 12.6% in children who underwent colonoscopy. Lucarelli et al. [17] reported an increased ratio in Italian children, i.e., 36%. In previous studies, the frequency of LNH varied between 10 and 30%, with variation depending on the terminal ileum intubation, colonoscopy indications, and study design (e.g., including only isolated LNH) [10].

Although LNH is considered a physiological condition, the association of LNH and FH has also been extensively studied. The association is more evident in colonic LNH when compared to LNH localized to the terminal ileum. Mansueto et al. [3] reviewed the link between LNH and FH, and found that approximately 66% of patients with LNH had FH and 49% of patients with FH had LNH. The most common symptoms in patients with LNH associated with FH are chronic abdominal pain, chronic diarrhea, hematochezia, and a failure to thrive. Increased levels of lamina propria γδ+ T cells can be detected in histopathologic examinations of the patients [18]. Generally, patients are of school age or preschool age, and have multiple food allergies and elevated serum anti-β-lactoglobulin IgG [3, 19].

Lucarelli et al. [17] reported a weak association between LNH and FH. They divided the isolated LNH patients into 3 groups randomly: an elimination diet group (cow’s milk, eggs, and foods positive on skin prick tests), a mesalamine group, and a symptomatic treatment group. At the end of the 8-week treatment, there was no significant difference in response to treatment among the groups. No association was found between the treatment response and the clinical, endoscopic, and allergic features of the patients. In our study, 37.8% of the patients with LNH had FH. The lack of a double-blind placebo control challenge test or control colonoscopic examinations made the diagnosis of food allergy in our patients questionable, but the symptoms of all patients improved after the elimination diet. We suggest that LNH is a manifestation of FH. It is also a common finding in allergic proctocolitis and non-IgE-mediated food allergy in infants. Our study did not indicate an association between LNH and non-IgE-mediated food allergy in older children.

A study performed at our center revealed that LNH is the most common colonscopic finding (27.8%) in patients with FMF [20]. Another study reported that FMF is responsible for LNH etiology in 15% of patients [11]. All the patients had compatible clinical findings and the diagnosis was confirmed by genotype analysis in these patients. Additionally, the authors showed that patients with FMF-related LNH had higher sedimentation rates and C-reactive protein levels, and more perianal lesions compared the patients without FMF. All of them were treated with colchicine treatment [11]. In our study, 7 patients (10.6%) had FMF and 5 of these received colchicine treatment. Two patients were diagnosed during the follow-up. Interestingly, 4 patients (6.1%) with LNH had a heterozygote MEFV genotype. We suggest that low-grade intestinal inflammation may persist in patients with FMF despite treatment and, in addition, low-grade intestinal inflammation may present in individuals with the heterozygote genotype. It has been shown that patients with FMF on colchicine treatment have increased levels of fecal calprotectin compared to healthy controls, suggesting...
low-grade intestinal inflammation [21]. Increased inflammatory symptoms have been found in individuals with a heterozygote MEFV genotype [22].

LNH of the colon and bulbus is a common finding with primary immunodeficiency, especially CVID and selective IgA deficiency [23]. In adults, LNH was found in 20% of patients with combined immunodeficiencies [11, 24]. But data on pediatric patients are scarce. Gurkan et al. [11] reported that the frequency of immunodeficiency associated with isolated LNH is 2.5%. In our study, we found it was 6.1%. Opportunistic chronic parasitic or viral infections may lead to the gastrointestinal symptoms and development of LNH in patients with immunodeficiency.

IBS is another cause of LNH in children. Approximately 15% of our patients with LNH were diagnosed with IBS based on the clinical diagnostic criteria. In adults, approximately 1/3 patients with IBS-type symptoms or suspected IBD present with diffuse colonic LNH. IBD and IBS are suggested to be different presentation of the same pathology. “Minimal lesion colitis,” also called colonic LNH is a common feature of IBS, IBD, Ni-allergy syndrome and other conditions such as hypersensitivity reactions, immunodeficiency, and chronic gastrointestinal infections. The factors and pathogenesis involved in the development of different clinical features from the same pathology are still under evaluation [25].

The association between LNH and chronic parasitic infections such as giardiasis were reported in previous studies. The presence of both giardiasis and hypogammaglobulinemia may cause the development of LNH. In our study, giardiasis and oxyuriasis were shown in a minority of patients but none of them had hypogammaglobulinemia.

Conclusion

We found that LNH may be related to many diseases such as FH, FMF, IBS, and immunodeficiency in children. Elimination of the triggering foods improved symptoms in patients with FH. The association of LNH and FMF is interesting, and FMF should be included in the list of causative factors of LNH especially in the presence of other clinical findings. Sometimes LNH may be a response to functional problems such as chronic constipation and diarrhea.

Statement of Ethics

Patients in the study have given their written informed consent and that the study protocol was approved by the institute’s committee on human research (study No. 2018/285).

Disclosure Statement

The authors have no conflicts of interest to declare.

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Author Contributions

M.C. and E.S. designed and wrote the manuscript; I.S. and F.O. did the clinical examinations.

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