Prevalence and Clinical Significance of *Helicobacter Pylori* Negative Chronic Gastritis in Children

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Abstract

Objectives: The clinical significance of *Helicobacter pylori* negative chronic gastritis (HPNCG) in children is unclear. We examined this issue in patients who had undergone esophagogastroduodenoscopy with systematic gastric sampling.

Methods: Data of 1,178 consecutive children who underwent diagnostic esophagogastroduodenoscopy were collected. Baseline characteristics and long-term outcomes were compared between children with active and inactive HPNCG and those with normal gastric histology. Follow-up data were available for up to 13 years.

Results: Altogether 24 (2.0%) children had active and 235 (19.9%) inactive HPNCG, 27 (2.3%) were H. pylori positive, 46 (3.9%) had other gastric pathology, and 846 (71.8%) normal histology. Diarrhea (31.3% vs. 25.1%, p=0.033), poor growth (23.6% vs. 14.7%, p<0.001), bloody stools (13.9% vs. 7.2%, p<0.001), anemia (46.5% vs. 23.4%, p<0.001), hypersedimentation (39.7% vs. 21.4%, p<0.001), hypoalbuminemia (40.4% vs. 16.2%, p<0.001) and elevated fecal calprotectin (62.4% vs. 31.5%, p<0.001) were more common and heartburn (13.9% vs. 22.9%, p=0.002) less common in the HPNCG group than in the controls. Both active (OR 3.64, 95% CI 1.35-9.82) and inactive (2.98, 2.18-4.08) HPNCG predicted a diagnosis in the initial investigations. Crohn's disease (41.7%) was the most common diagnosis in active HPNCG and celiac disease (37.4%) in inactive HPNCG. During follow-up, 7 (9.9%) of the 71 initially non-diagnosed HPNCG children received a diagnosis.

Conclusions: HPNCG is a frequent finding in children undergoing EGD, the active form being associated especially with Crohn's disease and the inactive with celiac disease. The long-term prognosis of patients with HPNCG who do not receive an initial diagnosis is good.

Keywords: Endoscopy, Gastric inflammation; Pediatric; Biopsy; *Helicobacter pylori*

What is known

- The incidence of *Helicobacter pylori* gastritis is declining rapidly in developed countries.
- *Helicobacter pylori* negative chronic gastritis (HPNCG) has become an increasingly recognized histological finding.
- The prevalence and clinical significance of HPNCG in children remains unclear.

What is new

- HPNCG is a common finding in pediatric esophagogastroduodenoscopy with systematically taken biopsies.
- HPNCG predicts a gastrointestinal diagnosis, particularly inflammatory bowel disease and celiac disease.
- The long-term prognosis of children with HPNCG without definitive initial diagnosis and without abnormal laboratory findings appears to be satisfactory.

Introduction

Gastritis denotes either acute or chronic inflammation of the stomach lining. Chronic gastritis is frequently asymptomatic and there is a poor correlation between endoscopic and histologic findings[1]. *Helicobacter pylori (H. pylori)* infection has traditionally been the leading cause of chronic gastritis in all age groups, while other external reasons, such as excessive consumption of alcohol or nonsteroidal anti-inflammatory drugs, which are common in adults, are considered less important in children[2, 3]. While still widespread in developing countries, *H. pylori* is becoming rare in developed countries. Simultaneously, the finding of *H. pylori* negative chronic gastritis (HPNCG) appears to be increasing[3, 4].

HPNCG remains poorly defined. It has been investigated mainly in connection with selected gastrointestinal conditions, such as inflammatory bowel disease (IBD) and celiac disease[3, 5–7]. The scarcity of studies and often inconsistent biopsy sampling during esophagogastroduodenoscopy (EGD) have hampered the evaluation of the prevalence, main causes, and clinical relevance of HPNCG. Simultaneously, the growing use of EGDs in children[8, 9] makes this histological finding an increasingly important clinical dilemma. It is particularly unclear whether HPNCG, either incidental or when associated with a specific condition, should be carefully monitored, and if its presence and subtype are relevant for the differential diagnostics of gastrointestinal diseases[10, 11].

Our institute has a long tradition of systematic gastric sampling during all pediatric endoscopies, which, together with systemically maintained patient records, provided us with an excellent opportunity to study the prevalence and long-term significance of HPNCG in a large cohort of consecutive children who had undergone EGD.

Materials and Methods

Patients and study design

The study was carried out at Tampere University and Tampere University Hospital. Comprehensive medical data on all children (age ≤17 years, n=2,394) who had undergone consecutive gastrointestinal endoscopies between January 2007 and October 2014 were collected from electronic patient records (Fig. 1). Patients with repeat endoscopy or colonoscopy only were excluded, and children with diagnostic EGDs with gastric sampling, with or without concomitant colonoscopy, were included (Fig. 1). The subjects included were categorized to those with and without any gastric pathology, and the former further to those with active HPNCG or inactive HPNCG, other type of gastritis or gastropathy (Fig. 1). Children with HPNCG formed the affected study group and those with normal gastric histology the control group. Besides medical information before and at the time of the endoscopies, long-term surveillance data spanning up to 13 years was collected.

The Department of Pediatrics at Tampere University Hospital approved the study design and collection of medical data. All analyses were conducted anonymously. According to on our national legislation, no approval of the Ethical committee was needed because the study was registry-based and none of study patients were contacted.

Clinical and laboratory data

Demographic information and symptoms and signs preceding the gastrointestinal endoscopies were collected from all study children, likewise possible gastrointestinal diagnoses set either in the course of primary investigations or during subsequent follow-up. The following laboratory results were also collected as available: blood hemoglobin (Hb, pediatric reference values from 100-141 g/l to 130-160 g/l), erythrocyte sedimentation rate (ESR, <15mm/h), plasma albumin (from 35-46 g/l to 37-51 g/l), plasma C-reactive protein (CRP, <10mg/l), serum endomysium (EmA, titer 1: <5), transglutaminase 2 antibodies (TGA, <7.0 U/L), and fecal calprotectin (<100 µg/g).[12]

Endoscopies and histopathology

A standard endoscopy protocol was adhered to throughout the study period. The protocol involved systematic description of the endoscopic abnormalities,[9] which could be utilized to target additional mucosal biopsies and to promote diagnostic reasoning. Furthermore, at least two representative forceps biopsies were taken from the esophagus, gastric body, and antrum, and at least four biopsies from the duodenum. Since 2012, biopsies have also been taken systematically from the upper part of the esophagus and the duodenal bulb[13]. Correspondingly, a minimum of two mucosal samples were taken from the rectum, sigmoid/descending colon, ascending colon, cecum, and terminal ileum in colonoscopy. In both EGD and colonoscopy, additional specimens were taken if clinically indicated.

The endoscopically obtained biopsies were cut, stained, and evaluated by pathologists with expertise in the alimentary tract. Histological grading of the gastric findings was based on the modified Sydney system[14]. HPNCG was identified as a characteristic inflammatory infiltration of mononuclear leukocytes and possibly a small number of eosinophils in the gastric mucosa and further classified into inactive and active forms, epithelial infiltration of neutrophilic granulocytes marking the latter[14]. Other gastritides (including *H. pylori* positive gastritides, eosinophilic, lymphocytic, granulomatous, and collagenous gastritis, gastritis with mast cells or acute gastritides, such as hemorrhagic and erosive gastritides) and non-inflammatory mucosal abnormalities indicating gastropathies were excluded from the main analysis. The categorization of other gastritides was based on the predominant cell types in the intraepithelial layer, while granulomas reminiscent of Crohn's disease defined granulomatous gastritis, dense collagen bands defined collagenous gastritis and hemorrhagic and erosive gastritides were considered to be acute gastritides[1, 11, 14–20]. *H. pylori* infection was confirmed histologically applying standard cultivation and staining methods[14, 20]. Gastric pathology

without significant inflammatory component was called gastropathy[19]. Subjects without any of the aforementioned findings in the stomach and those with only very minor unspecified histological findings (e.g. a few inflammatory cells graded by pathologists as normal variants) were included in the normal mucosa control group.

Statistical analysis

Clinical characteristics and prevalence of abnormal laboratory parameters and histologic findings are presented as percentage distributions, except for age, which is presented as medians with ranges. Statistical significance in qualitative parameters was calculated by chi-square or Fisher's exact test and in quantitative parameters by Mann-Whitney test as appropriate. The associations between diagnoses and active or inactive HPNCG were calculated using binary logistic regression analysis and expressed as odds ratios (OR) with 95% confidence interval (CI). To evaluate possible secular changes, the proportions of active and inactive HPNCG and *H. pylori* from all EGDs were calculated separately for each year. All statistical analyses were performed using SPSS Statistics version 25 (IBM Corp., Armonk, NY, USA). A p value ≤ 0.05 was considered significant.

Results

Gastric biopsies were available from all but three (99.7%) of the 1,181 children who underwent diagnostic EGD (Fig. 1). Of these, 1,161 (98.6%) had samples from both corpus and antrum. Abnormal gastric histology was reported in 332 (28.2%) of subjects, of whom 235 (70.8%) had inactive and 24 (7.2%) active HPNCG, 27 (8.1%) *H. pylori* gastritis, 32 (9.6%) other gastritis, and 14 (4.2%) gastropathy (Fig. 1). The main characteristics of these groups are presented in Supplementary Table 1. The number of children with HPNCG and *H. pylori* remained relatively

stable throughout the study period, although in recent years *H. pylori* has become almost non-existent and the presence of active HPNCG has slightly increased (Supp. Fig. 1).

Of all 259 HPNCGs, 51 (23.6%) were located in the antrum, 52 (20.1%) in the corpus, and 146 (56.4%) in both. Active HPNCG was significantly more frequently located in both antrum and corpus compared to inactive HPNCG (83.3% vs. 53.6% respectively, p=0.005) and less often in corpus alone (0% vs. 22.1%, p=0.006).

Children with active or inactive HPNCG presented more often with diarrhea, poor growth, bloody stools, elevated fecal calprotectin, hypersedimentation, anemia, and hypoalbuminemia and less often with heartburn (Fig. 2A and 2B) and were more likely to receive a diagnosis than children with normal gastric mucosa (Table 1). There was no difference in the frequency of diagnoses between active and inactive HPNCG (79.2% vs. 71.9%; p=0.448). Compared to patients with normal gastric mucosa, both active and inactive HPNCG were associated with Crohn's disease and inactive HPNCG also with celiac disease and ulcerative colitis (Table 1), which were also the most common diagnoses in the groups (Supplementary Fig. 2).

Children who had active HPNCG and received a diagnosis were older and presented more often with poor growth and hypersedimentation than those not receiving a diagnosis (Table 2). Also, children with inactive HPNCG and a diagnosis presented more often with poor growth and any laboratory abnormality, anemia, positive celiac serology, and elevated fecal calprotectin, and less often with any clinical symptom and heartburn than those not receiving a diagnosis (Table 2).

In the subgroup analyses, 295 of all children who underwent EGDs had celiac disease and HPNCG was detected in 93 of them. Children with celiac disease and concomitant HPNCG had more often anemia (52.9% vs. 35.0%, p=0.033) than those with normal gastric histology. Among altogether 121 children with inflammatory bowel disease, 66 had HPNCG

and presented more often with poor growth (42.4% vs. 21.8% p=0.016) and hypoalbuminemia (51.2% vs. 22.9%, p=0.011) and less often with constipation (3.0% vs. 14.5%, p=0.042) than children with normal gastric mucosa.

During a median follow-up time of six years, a later diagnosis was received based on repeated EGD or other investigations by one initially undiagnosed child with active HPNCG (*H. pylori* gastritis) and six with inactive HPNCG (two celiac diseases, mastocytosis, wheat allergy, cow's milk allergy, gastroesophageal reflux disease). At the time of the initial endoscopies abnormal laboratory values (positive celiac serology, elevated ESR, low albumin) were found in four and histologic abnormalities outside the stomach (lymphatic hyperplasia in the ileum and mild esophagitis, chronic inflammation in the bulbus) in two of the patients later receiving a diagnosis. Both of the children who later received a celiac disease diagnosis presented initially with positive celiac disease serology, but not yet duodenal atrophy, and thus did not yet start a gluten-free diet[13]. There were no significant differences in the baseline clinical or laboratory parameters between children who did and did not eventually receive a diagnosis (data not shown).

Discussion

We found HPNCG to affect 22% of consecutive children who underwent EGD with systematic gastric sampling. In contrast, other gastric abnormalities were infrequent and *H. pylori* gastritis affected only 2.3% of the patients. Further, during the eight years (2007–2014) of our study, the prevalence of both HPNCG and *H. pylori* gastritis remained fairly constant. The prevalence of *H. pylori* negative gastritis in pediatric EGDs has previously been reported to be between 37% and 94%. Available studies have usually included all gastritides and/or gastroparesis, not just chronic forms as is the case in our study[3, 4, 21, 22]. The focus of previous studies has been mainly on *H. pylori* positive gastritides with report of *H. pylori* negative findings[23, 24]. Of

importance, a significant decrease in *H. pylori* positive gastritis has been reported in many longitudinal studies published 1991-2009, likely reflecting the improved socio-economic environment in high and moderate-income countries[25–29]. In line with our findings, Genta and colleagues reported no changes in the prevalence of *H. pylori* positive gastritides between 2008 and 2014 in a US cohort including both children and adults, and in gastritis subgroups a prevalence of 1–2% for active HPNCG[30]. Altogether, the prevalence of both *H. pylori* negative and positive gastritis appears to have become more stable during the past decade, although there is wide variation between studies, possibly reflecting differences in histopathological classifications and a lack of systematic biopsy sampling. Although exact numbers are lacking, in our clinical routine *H. pylori* positive gastritis is significantly overrepresented among immigrant and adopted children.

One explanation for the temporal change from *H. pylori* positive to negative in the distribution of pediatric gastritides reflected in the aforementioned studies could be the rising prevalence of pediatric IBD[31–33] and celiac disease[34–36], in which HPNCG is known to be a common finding[5–7, 37–39]. We found both forms of HPNCG were associated with Crohn's disease and the inactive form was also associated with celiac disease and ulcerative colitis. Yet, it should be noted that the prevalence of *H. pylori* positive gastritides is shown to be higher in IBD and celiac disease patients in other countries[5,7], which may make it difficult to differentiate if the patient's gastritis is related to the *H. pylori* infection or to the baseline disease. Furthermore, IBD and celiac disease related symptoms[13, 40] were particularly common in patients with HPNCG and diagnoses. In a more detailed subgroup analysis, presence of HPNCG in celiac disease patients was associated with anemia and in those with IBD it was associated with failure to thrive and hypoalbuminemia indicating that HPNCG may be associated with severe disease features. The fact that children with inactive HPNCG without

diagnosis had higher frequency of any clinical symptom could be explained by the commonly reported unspecific symptoms such as abdominal pain or heartburn.

We found later diagnosis to be rare (9.9%) in HPNCG children who did not receive a diagnosis during the initial diagnostic work up with EGD and other diagnostic investigations. Moreover, up to 57% of those who received a diagnosis during later surveillance already had abnormal laboratory finding(s) at baseline. These findings included positive celiac serology without duodenal atrophy marking a potential celiac disease, elevated ESR, and low albumin which generally prompt the clinician to proceed with gastrointestinal endoscopy and further investigations as well as to keep a close follow-up[9, 41–44]. These findings suggest that children with HPNCG finding on gastric biopsies without initial diagnosis seem to do well. However, follow-up is important particularly in patients with abnormal laboratory findings at baseline.

The main strength of our study was the large cohort of consecutive children who had undergone EGD with exceptionally systematic sampling from esophagus, stomach and duodenum regardless of the endoscopy indication. Furthermore, we were able to collect comprehensive long-term follow-up data, although only six repeated EGDs were conducted on children with unexplained HPNCG due to the high threshold for this procedure in this age group. Of note, extensive examinations of pediatric gastrointestinal disorders are centralized to the study centre, thereby reducing the risk of missing any major diagnoses or progressing conditions. The retrospective design was a clear weakness, as it inevitably leads to less systematic measurement of laboratory parameters and recording of the symptoms. Partly due to this, the number of variables that could be included in some of the sub-group analyses was low, thereby reducing the statistical power. The heterogeneity of the results might have been further increased by the involvement of several gastroenterologists performing the EGDs and pathologists interpreting the gastric histology. However, the impact of this was reduced by our

long-term aim at consistent training of these professionals as recommended by international guidelines[9, 14], as well as routine discussion of problematic cases in multidisciplinary expert meetings including an experienced pathologist. Additionally, it should be noted that the *H. pylori* detection in the gastric samples could have been obscured due to patchiness of the infection, or due to possible proton pump inhibitor or antibiotic exposure. Finally, the fact that the study was carried out at a single tertiary center in a high-income country may impair the generalizability of our results, particularly to settings where autoimmune conditions remain less common and infectious gastritides still prevail[26].

In conclusion, HPNCG is a frequent histopathological finding in children undergoing EGD with systematic biopsy sampling regardless of various clinical indications. It is most often associated with a gastrointestinal diagnosis, the active form particularly associated with Crohn's disease and the inactive form with IBD in general and celiac disease. In IBD and celiac disease the presence of HPNCG may be associated with more severe clinical features. HPNCG without concomitant abnormal laboratory findings or established diagnosis does not seem to have prognostic significance.

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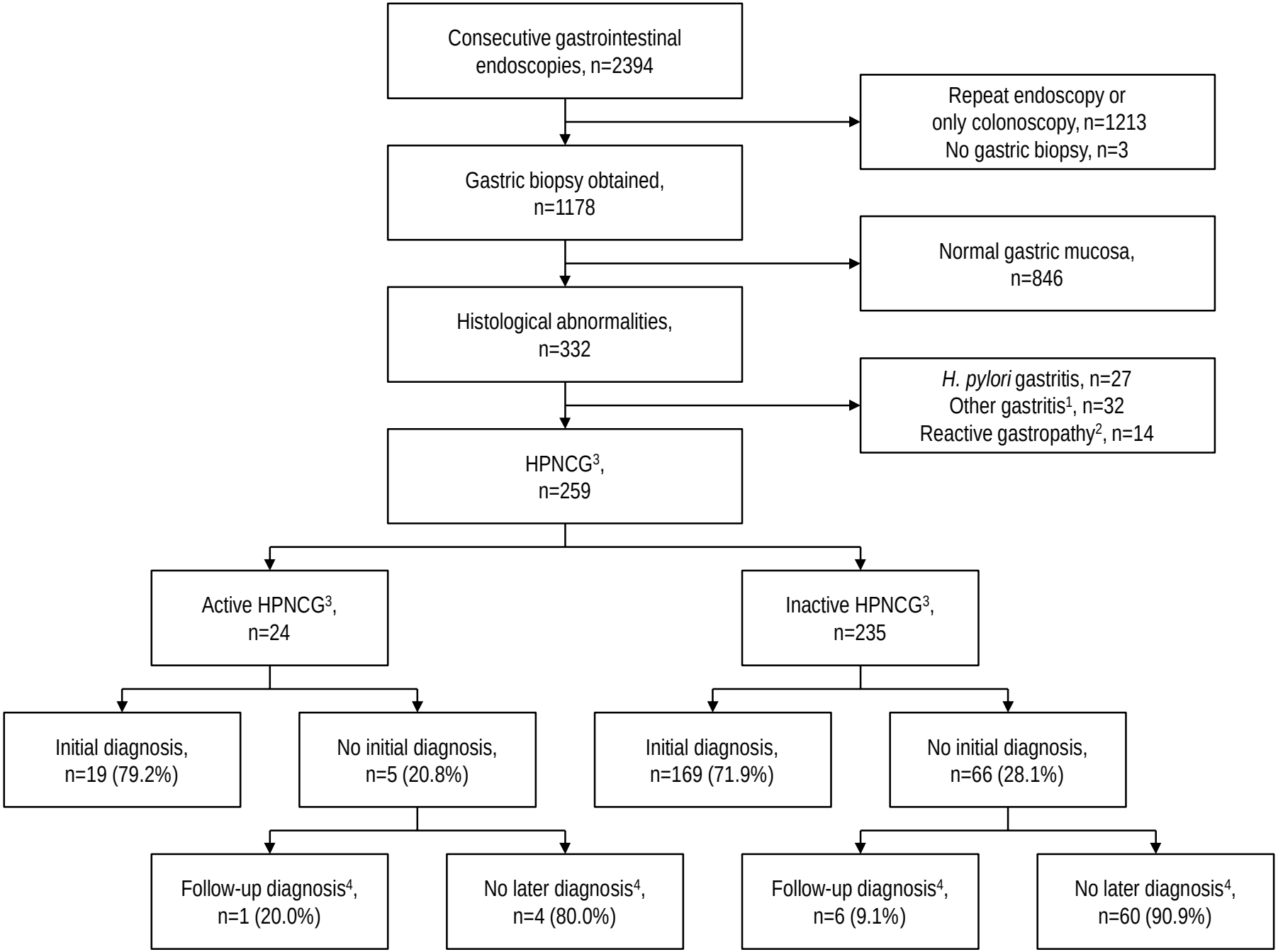
Figure legends

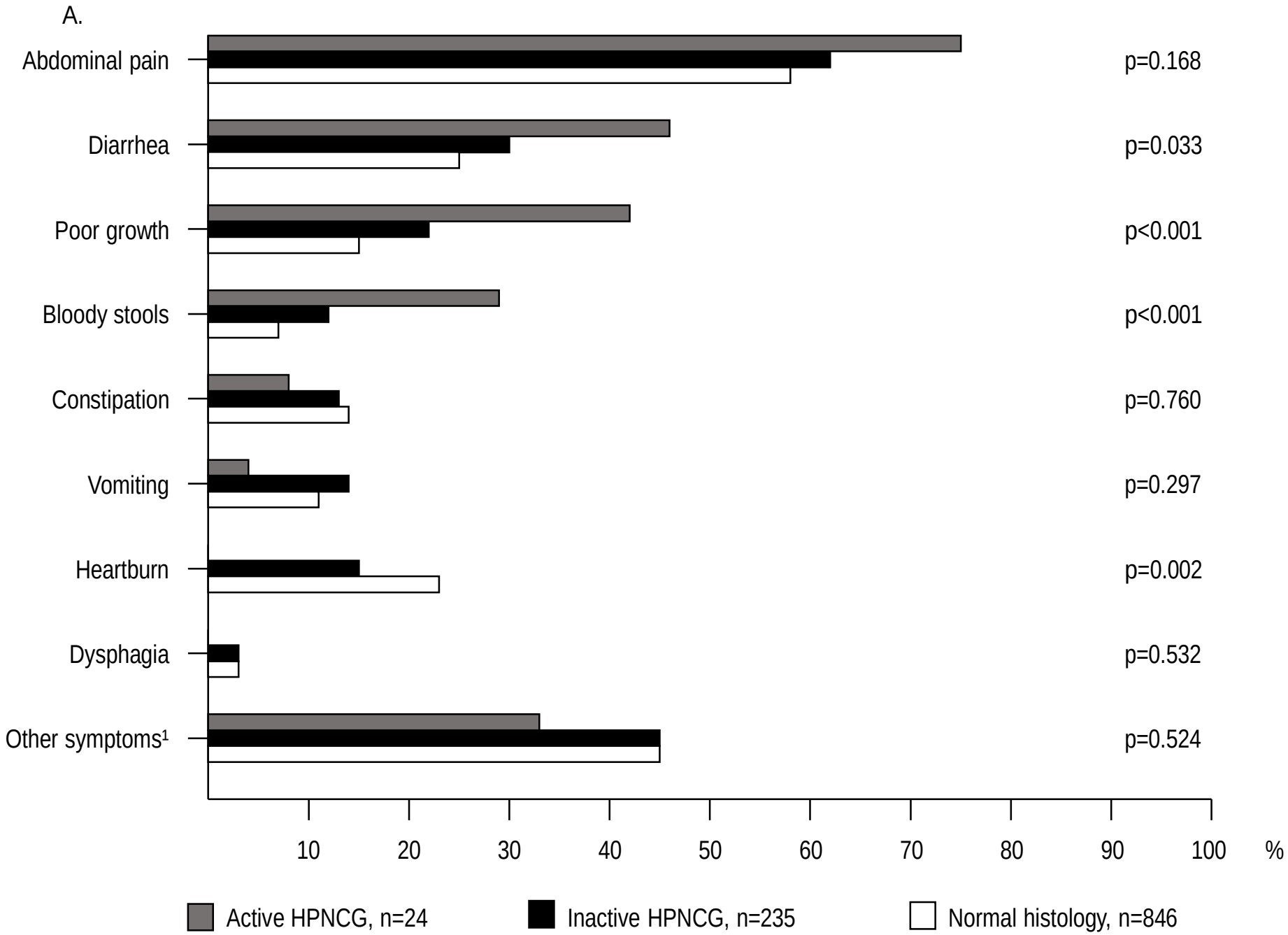
Figure 1. A flowchart of the study. [1]Eosinophilic, lymphocytic, granulomatous, and collagenous gastritis or gastritis with mast cells [2]Mucosal abnormalities without inflammation. [3]HPNCG, *H. pylori* negative chronic gastritis. [4]Follow-up up to 11 years.

Figure 2. A. Comparison of the prevalence of different symptoms between children with active or inactive *H. pylori* negative chronic gastritis (HPNCG) and normal gastric histology. P-values were calculated between all three groups. [1]E.g., nausea, flatulence, poor appetite, fatigue. **B.** Comparison of the prevalence of abnormal laboratory values between children with active or inactive *H. pylori* negative chronic gastritis (HPNCG) and normal gastric histology. P-values were calculated between all three groups. CRP, C-reactive protein; Laboratory values were available in 29.7-87.5% of cases. [1]Endomysium or transglutaminase 2 antibodies. Values in bold face indicate statistically significant differences.

Supplementary Figure 1. Secular changes in the prevalence of inactive and active chronic *H. pylori* negative gastritis (HPNCG) and *H. pylori* positive gastritis over eight years.

Supplementary Figure 2. Distribution of clinical diagnoses received in the initial investigations in children with active or inactive *H. pylori* negative chronic gastritis (HPNCG) and normal gastric histology. GERD, gastroesophageal reflux disease. [1]E.g., inflammatory bowel disease unclassified, gastrointestinal food allergy, mastocytosis.


Consecutive gastrointestinal endoscopies, n=2394
Repeat endoscopy or only colonoscopy, n=1213
No gastric biopsy, n=3
Gastric biopsy obtained, n=1178
Normal gastric mucosa, n=846
Histological abnormalities, n=332
H. pylori gastritis, n=27
Other gastritis[1], n=32
Reactive gastropathy[2], n=14
HPNCG[3], n=259
Active HPNCG[3], n=24
Inactive HPNCG[3], n=235
Initial diagnosis, n=19 (79.2%)
No initial diagnosis, n=5 (20.8%)
Initial diagnosis, n=169 (71.9%)
No initial diagnosis, n=66 (28.1%)
Follow-up diagnosis[4], n=1 (20.0%)
No later diagnosis[4], n=4 (80.0%)
Follow-up diagnosis[4], n=6 (9.1%)
No later diagnosis[4], n=60 (90.9%)


A.
Abdominal pain
Diarrhea
Poor growth
Bloody stools
Constipation
Vomiting
Heartburn
Dysphagia
Other symptoms[1]
p=0.168
p=0.033
p<0.001
p<0.001
p=0.760
p=0.297
p=0.002
p=0.532
p=0.524
10
20
30
40
50
60
70
80
90
100
%
Active HPNCG, n=24
Inactive HPNCG, n=235
Normal histology, n=846

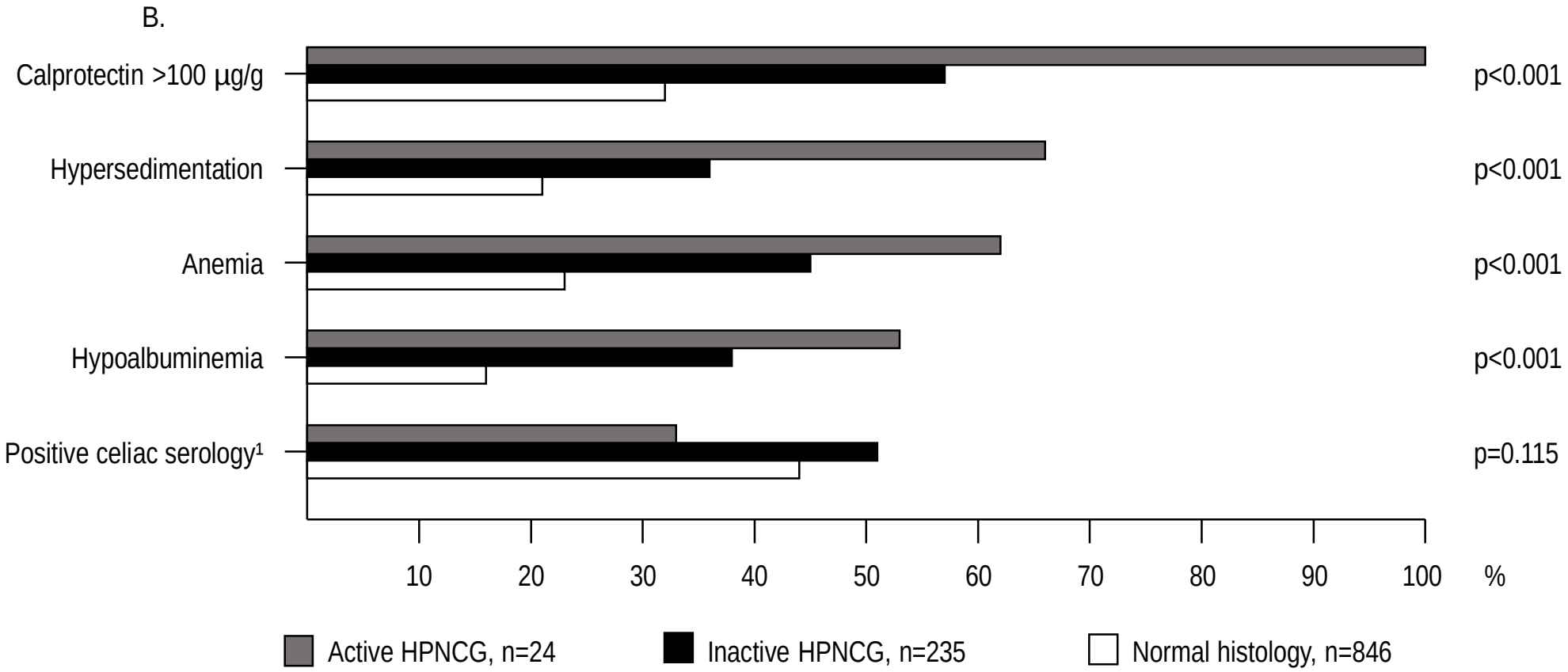

B.
Calprotectin >100 µg/g
Hypersedimentation
Anemia
Hypoalbuminemia
Positive celiac serology[1]
p<0.001
p<0.001
p<0.001
p<0.001
p=0.115
10
20
30
40
50
60
70
80
90
100
%
Active HPNCG, n=24
Inactive HPNCG, n=235
Normal histology, n=846

Table 1. Likelihood of o receiving a diagnosis during the initial investigations in children with active or inactive *H. pylori* negative chronic gastritis (HPNCG) compared to those with normal gastric mucosa.

	Celiac disease		Crohn's disease		Ulcerative colitis		GERD		Any diagnosis	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Normal mucosa	1		1		1		1		1	
Active HPNCG	0.84	0.31-2.28	**39.6**	**15.2-103**	3.41	0.97-12.0	0.48	0.06-3.62	**4.59**	**1.70-12.4**
Inactive HPNCG	**1.91**	**1.40-2.60**	**3.78**	**1.82-7.85**	**3.63**	**2.18-6.05**	0.76	0.42-1.35	**3.10**	**2.26-4.24**

CI, confidence interval; GERD, gastroesophageal reflux disease; OR, odds ratio; Values in bold face indicate statistically significant difference.

Table 2. Characteristics of 259 children with either active or inactive *H. pylori* negative chronic gastritis (HPNCG) who did and did not receive a diagnosis at the initial endoscopic and other evaluations

	Active HPNCG, n=24			Inactive HPNCG, n=235		
	Diagnosis n=19	No diagnosis n=5	P value	Diagnosis n=169	No diagnosis n=66	P value
Demographic data						
Age, median (range), year	12.3 (3.4,16.4)	7.1 (0.4,13.7)	**0.051**	9.1 (0.1, 15.8)	8.9 (0.2, 15.9)	0.927
Girls, %	63	80	0.631	62	53	0.201
Symptoms, %						
Any clinical symptom	95	100	1.000	91	98	**0.046**
Abdominal pain	79	60	0.568	58	71	0.061
Failure to thrive	53	0	0.053	26	11	**0.010**
Diarrhea	47	40	1.000	28	33	0.458
Bloody stools	32	20	1.000	14	8	0.165
Constipation	5	20	0.380	12	15	0.493
Vomiting	0	20	0.208	11	20	0.089
Heartburn	0	0	-	12	24	**0.018**
Other[1]	37	20	0.631	43	49	0.464
Laboratory values, %						
Any laboratory abnormality	100	80	0.208	92	74	**<0.001**
Calprotectin >100µg/g	100	ND	-	69	30	**0.002**
Hypersedimentation	86	0	**0.005**	40	26	0.147
Anemia	65	50	0.618	53	24	**0.001**
Hypoalbuminemia	58	33	0.569	42	27	0.223
Positive celiac serology[2]	39	0	0.524	62	16	**<0.001**
C-reactive protein >10 mg/l	36	25	1.0	15	7	0.334

[1]E.g. nausea, flatulence, poor appetite, fatigue, eczema; [2]Antiendomysial or transglutaminase 2 antibodies; Demographic and symptom data was available from all children and laboratory values from 30.2-89.5% except calprotectin from none of the active HPNCG children without diagnosis; Values in bold face indicate statistically significant difference; ND, no data.