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Diagnostic findings and long-term prognosis in anemic children undergoing gastrointestinal endoscopies

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Abstract

Background and Aims: Intestinal diseases are regarded as a common cause of anemia, but the diagnostic outcomes of anemic children undergoing endoscopic investigations are unclear. We investigated this issue in a large cohort of children.

Methods: Indications for and findings of consecutive gastrointestinal endoscopies were collected. Clinical presentation and diagnostic outcomes were compared between anemic and non-anemic patients, and between anemic patients with and without a diagnosis. Diagnoses received during follow-up were collected.

Results: Out of 2,395 consecutive endoscopies, 251 children with and 613 without anemia had undergone either diagnostic esophagogastroduodenoscopy (51.4% and 51.4% respectively), colonoscopy (4.0%, 11.4%), or both (45.8%, 37.8%). Anemic children more often received diagnoses (72.9% vs. 39.3%, OR 4.18, 95% CI 3.03-5.77), particularly of celiac disease (26.3% vs. 15.5%, $p<0.001$) and of inflammatory bowel disease (31.1% vs. 9.1%, $p<0.001$) than did non-anemic children. Diagnosis in anemic patients was predicted by age 5-12 years (OR 3.52, 95% CI 1.27-9.75), presence of diarrhea (2.04, 1.07-3.90), melena/hematochezia (2.40, 1.17-4.92), poor growth (3.94, 1.70-9.15), positive celiac serology (11.81, 3.47-40.12), high calprotectin (12.86, 4.00-41.32), hypersedimentation (2.65, 1.29-5.44), and hypoalbuminemia (5.05, 1.56-16.34). Thirty anemic children (12.0%) had no gastrointestinal symptoms and 22 of them (73.3%) were given diagnoses at the time of the endoscopies. All 22 presented with additional laboratory abnormalities, while these were present in only two of the eight undiagnosed children. None of them were diagnosed later in the follow-up of up to 11 years, in contrast to four (6.7%) of all anemic and 33 (8.9%) of non-anemic patients.

Conclusion: Anemia increased the probability of being given a diagnosis, emphasizing its importance as an alarm symptom. However, endoscopies in anemic patients without additional symptoms or laboratory abnormalities seldom improved the diagnostic yield.

Introduction

Anemia is one of the most common chronic medical problems in children, affecting on average 16.7% of preschool children in Europe and as many as 64.6% in Africa.[1] While in developing countries pediatric anemia is usually caused by inadequate nutrition and deficits of essential micronutrients, in developed countries the leading cause is iron deficiency, which may be either dietary or secondary to a gastrointestinal or hematological disease or other chronic condition.[2] It is important to bear in mind that anemia is not a diagnosis as such but a clinical sign, the underlying cause of which should always be investigated.

Alimentary tract diseases are regarded as a common reason for anemia. The development of anemia in these conditions is multifactorial, including e.g. insidious blood loss and inadequate iron absorption.[3,4] It has been suggested that gastrointestinal pathologies should always be ruled out in children and adolescents with unexplained anemia[5]. Unfortunately, a reliable examination of the intestine requires invasive methods, particularly esophagogastroduodenoscopy (EGD) and colonoscopy, which in children are usually performed under general anesthesia. Optimal targeting of these invasive procedures in children would be of particular importance, but currently the evidence on this issue is scarce.[6–9]

Materials and methods

Study ethics

The study design and data collection were duly approved by the Department of Pediatrics, Tampere University Hospital. All identifiable personal data was coded and analyses were performed anonymously. According to the national guidelines in Finland, this registry-based study required no ethical approval.

Patients and study design

The retrospective cross-sectional study of a tertiary center was conducted at Tampere University and Tampere University Hospital. We have long maintained comprehensive medical records on all children undergoing gastrointestinal endoscopies and performed systematic mucosal sampling irrespective of macroscopic findings. These practices afforded us an opportunity to investigate the diagnostic yield of endoscopic investigations and the long-term prognoses in children with unexplained anemia.

The medical data on children (age <17 years) who had undergone consecutive EGDs and/or colonoscopies in 2007-2014 was recorded. Only patients who had undergone diagnostic endoscopy/endoscopies and for whom anemia/hemoglobin data were available were included for further analyses while follow-up and other endoscopies (rectosigmoidoscopies) were excluded. These children were divided into anemic and non-anemic groups, and the anemia group further into those presenting with and without additional gastrointestinal symptoms (Figure 1). All study data was compared between these groups. Further, patient characteristics predicting diagnosis were identified. Besides medical information before and at the time of the endoscopic studies, follow-up data was collected from two to 11 years.

Clinical and laboratory data

The information recorded included demographic parameters, clinical presentation, duration of symptoms, presence of poor growth, chronic conditions, and family history of gastrointestinal diseases. Other possibly conducted relevant investigations of the gastrointestinal tract, such as wireless capsule endoscopy (WCE), magnetic resonance enterography or esophageal pH monitoring, were also recorded, likewise all diagnoses set in either the primary or follow-up investigations. Children with minor unspecific and apparently clinically insignificant endoscopic or histological abnormalities, such as lymphonodular hyperplasia common in

children or inactive chronic gastritis, and those with only functional abdominal symptoms were assigned to the no-diagnosis group.

The results of the following laboratory tests were collected as available: blood hemoglobin and mean corpuscular volume (Hb and MCV, reference values (Rf)[10] presented in Supplementary table 1.), plasma ferritin (Rf > 6 µg/l), plasma transferrin receptor (TfR, Rf for children <1 yrs 1.6-7.0 mg/l, 1-3 yrs 2.7-5.4 mg/l and 4-6 yrs 2.4-6.3 mg/l; for boys 7-12 yrs 2.4-5.7 mg/l, girls 7-12 yrs 2.0-5.1 mg/l, boys 13-17 yrs 2.0-6.8 mg/l, and girls 13-17 yrs 1.6-5.2 mg/l), erythrocyte sedimentation rate (ESR, Rf <15mm/h), plasma albumin (Rf from 35-46 g/l to 37-51 g/l), plasma alanine aminotransferase (ALT, Rf <40 U/l), serum anti-endomysial antibodies (EmA, Rf titer 1: <5) and IgA-class antibodies against transglutaminase 2 (TGA-IgA, Rf <7.0 U/L), and fecal calprotectin (Rf <100 µg/g).

In order to calculate the possible effect of the severity of anemia on the likelihood of a subsequent diagnosis, hemoglobin values at the time of endoscopy were further sub-classified using the World Health Organization criteria.[11]

Failure to thrive was defined as reduced growth velocity in the longitudinal evaluation of growth charts and/or impaired height or weight development when compared to the gender and age dependent reference values or to target height calculated using midparental height.[12]

Histology

Endoscopic abnormalities were reported systemically and photographed if considered potentially significant. During EGD at least two mucosal biopsies were taken systemically, regardless of the preceding clinical and laboratory findings, from the lower esophagus, antrum, and gastric corpus and antrum, and at least four biopsies from the duodenum. Since 2012 biopsies were also obtained from the duodenal bulb and middle part of the esophagus. During

colonoscopy biopsies were taken from the rectum, sigmoid/descending colon, ascending colon/cecum, and terminal ileum. In both EGD and colonoscopy, additional biopsies were taken as clinically indicated. The endoscopies were considered adequate when biopsies were taken systemically from each above-mentioned bowel section.[7] The biopsies were cut, stained, and evaluated by standard histopathology methods. If needed, special stainings were performed. Only representative and correctly oriented and cut histological specimens were accepted for quantitative morphometric analyses of duodenal samples.[13] All abnormalities reported by a pathologist were regarded as histologic findings even if not diagnostic, including, for example, unspecified duodenal inflammation, mildly increased number of eosinophils in the esophagus[14] and inactive chronic gastritis. The individual diagnoses were set according to international consensus[14–20] or, if no specific guidelines existed, based on previous literature and clinical experience. During the study period the European guidelines on celiac disease were revised in 2012 but the new criteria[21] were not implemented in our clinical practice until 2015. Additionally, the guidelines on food allergy[22] and H. pylori[23] were both updated in 2011 and the guidelines of reflux disease[24] in 2009, and the new criteria were subsequently used to establish the diagnoses. The diagnosis of gastrointestinal food allergy was set by experienced clinicians based on a combination of clinical and histological findings, allergy testing, and elimination diet followed by food challenge.[22]

Statistical analysis

Clinical characteristics, abnormal laboratory parameters and endoscopic and histologic findings are presented as percentage distributions. Statistical significances of differences in qualitative parameters were calculated using Chi-square test or Fisher's exact test. Most of the quantitative variables were found to be skewed by the Shapiro-Wilk method and included outliers. The variables were thus analyzed by non-parametric Mann-Whitney test and expressed as medians

and quartiles.[25] The associations between symptoms/clinical signs and diagnoses were calculated using binary logistic regression analysis with 95% confidence intervals (CI). The odds ratios (OR) were calculated comparing males with females, age groups with those younger than one year, and patients with autoimmune disease, intestinal disease in relatives, different symptoms or abnormal laboratory parameters with those without such findings. A p-value of <0.05 was considered statistically significant. All statistical analyses were performed using SPSS Statistics version 23 (IBM Corp., Armonk, NY, USA).

Results

Altogether 2,395 consecutive gastrointestinal endoscopies were conducted during the study period. Of these, 1,117 were follow-up or other endoscopies and 399 children lacked hemoglobin values and were therefore excluded. Of the remaining 864 children with hemoglobin/anemia data available, altogether 251 (29.1%) had anemia (Figure 1). Of these, 128 (51.0%) had undergone EGD alone, 10 (4.0%) had undergone colonoscopy alone and the other 113 (45.1%) had undergone both EGD and colonoscopy. The corresponding figures for non-anemic children were 311 (50.7%), 70 (11.4%) and 232 (37.8%). The duodenum was reached in 98.8% and 99.1% and the ileum in 65.3% and 67.1% of the anemic and non-anemic children respectively. Subsequently, combined with missing samples in some cases, respectively 83.0% and 85.1% of EGDs and 62.1% and 67.2% of colonoscopies of the anemic and non-anemic children were considered adequate according to our strict definition. Additional alimentary tract investigations were conducted on 93 (37.1%) anemic and 214 (35.0%) non-anemic children, including WCE in 22 (8.8%) and 37 (6.0%).

Children with anemia were significantly older (median 10.8 vs. 8.3 years, p=0.012) and had more often concomitant autoimmune disease, positive calprotectin, and low MCV than did those without anemia (Table 1). They also presented with higher TfR and ESR

and lower ferritin and albumin values (Table 1), whereas there were no differences between the groups in gender distribution, presence of other diseases, familial history, celiac antibody or ALT levels. Failure to thrive was significantly more common and abdominal pain, reflux, and dysphagia less common in anemic children (Figure 2). Anemic children also had more often endoscopic findings in both EGD (60.3% vs. 47.9%, p=0.001) and colonoscopy (72.1% vs. 48.3%, p<0.001), as well as histologic abnormalities at each biopsy site excluding the esophagus (Table 2).

Altogether 183 (73.0%) anemic and 241 (39.3%) non-anemic patients received a diagnosis during the primary investigations (OR 4.18, 95% CI 3.03-5.77) (Figure 1). Eight (80.0%) out of the 10 children with severe anemia, 91 (82.0%) out of the 111 children with moderate anemia, and 77 (64.7%) out of the 119 children with mild anemia received a diagnosis (p=0.011). Altogether, anemia had 43.2% sensitivity, 84.6% specificity, 72.9% positive predictive value, 60.7% negative predictive value and 64.2% overall accuracy for the subsequent diagnosis. Seven anemic children (2.8%) with normal histologic findings in EGD/colonoscopy received a diagnosis in other concomitant investigations, including one with Meckel's diverticulum in technetium scan and one with Burkitt's lymphoma in MRE. No endoscopic abnormalities were reported in 24 (13.1%) of the anemic and 59 (24.5%) of the non-anemic children who received a diagnosis.

Anemic patients with diagnoses presented more often with positive celiac serology, positive calprotectin, and had higher ESR and lower albumin values than those without diagnoses (Supplementary Table 2). Predictors for initial diagnoses in anemic patients were age from five to twelve years, presence of diarrhea, melena/hematochezia, poor weight gain, positive celiac antibodies, high calprotectin or ESR values, and hypoalbuminemia, whereas children with reflux symptoms were less likely to receive a diagnosis (Table 3). In non-anemic patients, symptoms significantly increasing the likelihood of diagnosis were

comparable to those in anemic patients excluding diarrhea and hypoalbuminemia (data not shown). In multivariate binary regression analysis, anemia, melena/hematochezia, and failure to thrive predicted diagnosis independently of other gastrointestinal symptoms (Supplementary Table 3).

An additional four anemic (1.6%) and 33 non-anemic (5.4%) cases received diagnoses later in follow-up (Figure 1). The follow-up diagnoses in anemic children were Crohn's disease, reflux disease (GERD), angiodysplasia and Imerslund-Gräsbeck syndrome, while in the non-anemic patients the most common diagnoses were celiac disease (n=9), Crohn's disease (n=6), GERD (n=5), and gastrointestinal food allergy (n=4).

The most common initial diagnoses in the anemia group were celiac disease and inflammatory bowel disease (IBD), which were also more common in anemic than in non-anemic patients (Figure 3). Other gastrointestinal diagnoses found in more than one anemic child were *H. pylori* gastritis (n=11), GERD (n=7), gastrointestinal food allergy (n=5), gastric or duodenal ulcer (n=3), juvenile polyps (n=2), and undefined colitis (n=2), whereas GERD (n=30), *H. pylori* gastritis (n=12), gastrointestinal food allergy (n=14), esophagitis (n=6), mastocytosis (n=5), pinworms (n=5), juvenile polyps (n=3), polyposis syndrome (n=2), gastric/duodenal ulcer (n=3), and rectal prolapse (n=2) were found in non-anemic children.

Of the anemic children 45 (17.9%) presented with only anemia-related laboratory abnormalities. Of these 23 (51.1%) had undergone EGD alone, two (4.4%) colonoscopy alone, and 20 (44.4%) both EGD and colonoscopy. Fifteen (33.3%) of them received a diagnosis in the initial investigations, including six IBD, one fungal esophagitis, three reflux esophagitis, one GERD diagnosed based on esophageal pH monitoring, two gastric/duodenal ulcers, one Burkitt's lymphoma, and one eating disorder. Two of the children received a diagnosis during subsequent follow-up (Crohn's disease and angiodysplasia).

Thirty anemic children had no additional gastrointestinal symptoms. All of them underwent EGD and seven also colonoscopy. Initial endoscopies revealed a diagnosis in 22 cases (Figure 1), including 13 celiac disease, four *H. pylori* gastritis, two IBD, one gastrointestinal stromal tumor, and one autoimmune gastritis. Additional laboratory abnormalities besides anemia and/or low MCV, were present in all 22 (Supplementary Table 4). None of the remaining eight children underwent repeated endoscopies or received a diagnosis during follow-up of up to 11 years (Figure 1). After the endoscopies a WCE was conducted in four of them and a technetium scan in two of them, with normal findings. One of them had elevated ESR (21 mm/h) and one elevated calprotectin (2160 μg/g) that later normalized. In six out these eight children the hemoglobin values normalized during iron supplementation.

Forty-four (7.2%) non-anemic children had signs of iron deficiency based on low MCV and/or ferritin value and/or high TfR value. Twenty (45.5%) of these patients received a diagnosis compared to 39% of the remaining non-anemic children (p=0.570).

Discussion

We found abnormal endoscopic and histologic findings at almost every biopsy location, as well as the number of final diagnoses, to be more frequent in anemic than in non-anemic children. In addition, the anemia group presented significantly more often with growth problems ($p<0.001$) and previously diagnosed autoimmune diseases (p=0.036) and, of the laboratory parameters, hypersedimentation, hypoalbuminemia, increased fecal calprotectin ($p<0.001$ each), and positive celiac antibodies with borderline significance (p=0.058). Co-occurrences of these symptoms and markers, alongside diarrhea and melena/hematochezia, were also those that further increased the likelihood of diagnoses in anemic children. Although classically considered an “alarm signal”, data on the actual significance of anemia when considering

pediatric gastrointestinal endoscopies has been limited.[5] More evidence on this issue is particularly important in children since, even if permanent adverse effects are relatively rare, these invasive and expensive procedures should be carried out only after careful assessment of the benefits and risks involved.[5,26]

Although studies with a similar design are lacking, our results can, to some extent, be compared with studies investigating the yield of gastrointestinal endoscopies at a more general level. In a small study by Wang et al.[9] anemia was the most common laboratory finding in children undergoing EGD and/or colonoscopy, and up to 75% of the 20 anemic subjects were found to have abnormal histology. Nevertheless, neither the prevalence of anemia in patients undergoing EGD nor histologic changes in non-anemic subjects were presented. Noble and colleagues[27] reported anemia, as well as rectal bleeding, hypoalbuminemia, and hypersedimentation to predict endoscopic and/or histologic findings in colonoscopy, whereas age ≥13 years, hematemesis, dys/odynophagia, vomiting and hypoalbuminemia, but not anemia, were associated with EGD abnormalities. Vomiting and dysphagia did not increase the likelihood of diagnoses here, but this may be due to the different study designs and the low frequency of these symptoms in our cohort. Moreover, in our settings systematic sampling from the middle part of the esophagus was not done before 2012. We also found anemic children between five and 12 years old to be more likely to be given a diagnosis than were older children. This is at least partially explained by the fact that the median age of anemic patients with celiac disease, our most common diagnosis, was 7.1 years. The constantly increasing number of pediatric IBD diagnoses may in the future change the age distribution.

Celiac disease and IBD were the most frequent cause for anemia in our study. This differs from reports from Turkey[28], Taiwan[29], Egypt[30], and Italy[3], where *H. pylori* gastritis (11-43%) and/or inadequate iron intake (16-39%) were the leading causes, while celiac disease was common (19%) only in the Italian study[3] and IBD reported only in one Taiwanese child[29].

Here dietary cause was rare and *H. pylori* was present in only 4.4% of the children, which likely reflects the improved nutrition, rapid decrease of *H. pylori* infection,[31–33] and the concurrent worldwide increase in immune-mediated diseases.[34] The differences observed between countries as the cause of pediatric anemia may thus reflect temporal variation in these changes. Interestingly, up to 16% of the Italian children with anemia were diagnosed with cow's milk allergy, the severe enteropathic form[35] of which we currently find exceptional.

The decision to proceed to endoscopy in children with suspicion of celiac disease or IBD is usually quite straightforward based respectively on either serology or on specific symptoms and high blood and fecal inflammatory markers. In fact, the symptoms and markers we found to best predict diagnoses in anemic children are the classic signs of these two conditions.[21,36] In these circumstances, the presence of anemia rarely influences the decision to perform endoscopy. Nevertheless, anemia predicts more severe histopathology in celiac disease[37–39] and could thus support EGD in cases with borderline positive serology. In case of IBD suspicion, the hemoglobin level may affect the urgency of endoscopies. Even though good non-invasive antigen tests for *H. pylori* are available,[40] and the infection is a possible cause of unexplained anemia, other causes of anemia should be ruled out before testing it by non-invasive or invasive methods.[41] Then again, many of the other possible causes can only be ruled out by endoscopic studies, including colonoscopy. This brings us to the broader question of when to perform only EGD or colonoscopy, and when both, on anemic children. The guidelines by the European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN), consider unexplained anemia to be an indication for both, but the evidence is scarce.[5] Resolving this issue was not among the aims of our study and further research on it is needed.

The decision on endoscopy is more difficult in the presence of less specific symptoms, and particularly when anemia is the sole presenting sign. We found co-existence of

constipation, abdominal pain or vomiting with anemia not to affect the likelihood of diagnoses, and reflux symptoms even reduced the probability. Consequently, uncomplicated reflux symptoms, "functional gastrointestinal disorders" and constipation as such are not indications for endoscopy in the ESPGHAN guidelines.[5] Evidence on the endoscopic yield in anemic children without any gastrointestinal symptoms is almost nonexistent, and we thus deem our results important. Notably, all 22 children without gastrointestinal symptoms who received a diagnosis presented with additional laboratory abnormalities, whereas these were (temporarily) present in only two of the non-diagnosed children. This suggests that in children with mild or moderate anemia as a sole clinical sign/laboratory finding, a short period of observation with possible iron supplementation could be a safe option, particularly as gastrointestinal malignancies are extremely rare in this age group. Instead, when "red flag" gastrointestinal symptoms such as melena/hematochezia or failure to thrive are present, an endoscopy and possible adjunct testing should be conducted even without anemia or other laboratory abnormalities.

The main limitations of the study are the retrospective design and data collection from only one tertiary center. Although the retrospective design enabled a large study cohort and a long-term follow-up, it limited our opportunities to evaluate the significance of individual laboratory parameters separately, since in clinical practice they, with the exception of almost always measured hemoglobin, are usually taken selectively based on the clinical scenario. This also hampered the opportunity to evaluate the subtypes of anemia, as well as children presenting with signs of iron deficiency despite normal hemoglobin. Another problem is that the pediatric reference values for iron-related parameters vary and remain controversial.[42–45] It is also important to realize that some laboratory parameters, such as anemia and ESR, may interact. These limitations were, however, counterbalanced by the large number of consecutive endoscopies with systematic biopsy sampling regardless of previous laboratory test results and

endoscopic findings, as well as by the availability of comprehensive medical information, including long-term follow-up data. The importance of systematic sampling is emphasized by the fairly high number of children receiving a diagnosis despite macroscopically normal endoscopy. The study population was also clinically and socio-economically diverse and represented all pediatric age groups. Although several endoscopists and pathologists were involved during the study period, the diagnostic heterogeneity should be reduced by our unified clinical practices and regular discussion of problematic cases in multidisciplinary meetings. It is nevertheless possible that the higher number of EGDs conducted in anemic children biased the results. Furthermore, some of the histological abnormalities reported may not have any major clinical relevance, and the percentage of ileum intubation rate was unacceptably low. It must also be mentioned that we did not evaluate the significance of fecal occult blood testing, as the benefits of this approach in children remain controversial.[46] Altogether, when considering the generalizability of our results, the substantial countrywide variation in the diagnostic approach to and etiology of anemia has to be kept in mind.[1]

To conclude, anemia increased the likelihood of a diagnosis in pediatric gastrointestinal endoscopies. However, in a subgroup of children with non-specific symptoms and no additional laboratory abnormalities, and especially with anemia as the sole presenting sign, a period of non-invasive surveillance with a possible treatment trial, might be considered. Furthermore, subsequent diagnosis after endoscopy with negative results appears to be exceptional even in the long-term.

CONFLICT OF INTEREST

Guarantor of the article: Kalle Kurppa, MD, PhD.

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Figure legends

Figure 1. A flowchart of the study. [1]A patient was considered anemic if the hemoglobin value was below the age- and sex-dependent reference at the time of endoscopy. [2]For up to 11 years of follow up. GI, gastrointestinal.

Figure 2. Comparison of the prevalence of different symptoms in children with and without anemia. Other symptoms included e.g. fatigue, persistent fever, and dermatological symptoms.

Figure 3. Comparison of the diagnoses received in the initial investigations between patients with or without anemia.

Tables

Table 1. Characteristics of 864 children with and without anemia at the time of their first gastrointestinal endoscopies.

	Anemia N=251		No anemia N=613		P value
Categorical variables	N	**%**	N	**%**	
Girls	135	53.8	326	53.2	0.872
Autoimmune disease[1]	20	8.0	27	4.4	0.036*
Asthma, allergy or atopy	44	17.5	116	18.9	0.632
Other chronic disease	32	12.7	58	9.5	0.151
Intestinal disease in relatives[2]	48	19.1	153	25.0	0.065
Positive EmA or TGA-IgA	70[3]	39.5	132[3]	31.5	0.058
Fecal calprotectin > 100µg/g	65[4]	69.1	84[4]	33.1	<0.001*
Low MCV	91[5]	42.3	38[5]	6.8	<0.001*
Continuous variables	No. of data	Median (quartiles)	No. of data	Median (quartiles)	
Age, years, (range)	251	10.8 (0.03, 16.7)	613	8.3 (0.02, 17.7)	0.012*
Ferritin, µg/l	62	7.5 (5.0, 15.3)	70	20.5 (13.8, 31.0)	<0.001*
Transferrin receptor 1, mg/l	58	7.2 (5.0, 14.5)	37	4.3 (3.7, 5.2)	<0.001*
ESR, mm/hr	168	12.0 (5.0, 25.75)	434	7.0 (5.0, 11.3)	<0.001*
Alanine aminotransferase, U/l	172	19.5 (14.0, 29.0)	399	17.0 (14.0, 24.0)	0.189
Albumin, g/l	102	36.0 (33.0, 40.0)	305	40.0 (37.0, 43.0)	<0.001*

[1]Type 1 diabetes, rheumatic or thyroidal disease, celiac disease; [2]Celiac disease or inflammatory bowel disease; [3]Data from 177 anemic and 419 non-anemic patients; [4]Data from 94 anemic and 254 non-anemic patients; [5]Data from 215 anemic and 557 non-anemic patients; *P-value≤0.050; EmA, anti-endomysial antibodies; ESR, erythrocyte sedimentation rate; MCV, mean corpuscular volume; TGA-IgA, IgA-antibodies against transglutaminase 2.

Table 2. Distribution of histologic abnormalities in the endoscopic biopsies of patients with and without anemia.

Biopsy location	Anemia N=251		No anemia N=613		P value
	No. of sampling	Abnormalities[1] %	No. of sampling	Abnormalities[1] %	
Total EGD	242	72.7	543	51.6	<0.001*
Esophagus	236	22.5	538	19.7	0.382
Stomach	241	49.0	542	26.8	<0.001*
Duodenum	239	36.8	538	22.1	<0.001*
Total colonoscopy	124	71.8	300	33.0	<0.001*
Ileum	81	28.4	208	13.5	0.003*
Ascending colon	110	60.0	274	20.4	<0.001*
Descending/sigmoid colon	122	62.3	297	21.5	<0.001*
Rectum	116	57.8	277	20.9	<0.001*

[1]Subjects could have histological abnormalities in one or more sampling site; EGD, esophagogastroduodenoscopy; *P-value≤0.050.

Table 3. Relationships between clinical features, presence of endoscopic and histologic findings, and diagnosis received in initial investigations in 251 anemic patients

		Abnormal findings		Diagnosis		
	No. of cases	Endoscopic %	Histologic %	%	Odds ratio[1]	95% CI
Sex						
Female	135	72.6	80.7	70.4	-	-
Male	116	80.2	82.8	75.9	1.32	0.75-2.32
Age						
<1 y	21	61.9	61.9	52.4	-	-
1-4 y	52	73.1	82.7	73.1	2.47	0.86-7.07
5-12 y	78	78.2	87.2	79.5	3.52	1.27-9.75
13-17 y	100	79.0	81.0	72.0	2.34	0.89-6.11
Autoimmune disease[2]	44	88.6	75.0	77.3	0.86	0.32-2.33
Intestinal disease in relatives[3]	48	81.3	85.4	79.2	1.52	0.71-3.25
Symptoms						
Abdominal pain	135	73.3	83.7	71.9	0.89	0.51-1.56
Diarrhea	82	84.1	92.7	81.7	2.04	1.07-3.90
Melena/hematochezia	69	89.9	89.9	84.1	2.40	1.17-4.92
Poor weight gain/growth	64	84.4	92.2	89.1	3.94	1.70-9.15
Constipation	38	71.1	76.3	65.8	0.29	0.32-1.40
Vomiting	26	73.1	73.1	69.2	0.82	0.34-1.98
Reflux	23	52.2	43.5	39.1	0.20	0.08-0.49
Other	101	80.2	82.2	74.3	1.12	0.63-1.99
Laboratory parameters						
Positive celiac serology[4,5]	70	80.0	97.1	95.7	11.81	3.47-40.12
Fecal calprotectin > 100µg/g[6]	29	87.7	95.4	92.3	12.86	4.00-41.32
Hyper sedimentation[7]	78	84.6	88.5	82.1	2.65	1.29-5.44
Hypoalbuminemia[8]	48	83.3	95.8	91.7	5.05	1.56-16.34

[1]Calculated by binary regression analysis with 95% confidence intervals (CI) comparing males with females, age groups with those younger than one year, and patients with autoimmune disease, intestinal disease in relatives, different symptoms or abnormal laboratory parameters with those without such findings; [2]Type 1 diabetes, rheumatic or thyroidal disease, celiac disease; [3]Inflammatory bowel disease or celiac disease; [4]Anti-endomysial antibodies or IgA-antibodies against transglutaminase 2; Data from [5]177, [6]94, [7]168 and [8]102 patients.

Supplementary Table 1. Finnish age- and sex -dependent pediatric reference values[10] for hemoglobin (Hb) and mean corpuscular volume (MCV).

	Hb, g/l	MCV, fl
1-7 days	150-230	88-126
7-30 days	100-206	85-123
1-2 months	95-130	80-103
2-6 months	95-141	76-97
6-12 months	100-141	72-87
1-2 years	100-142	73-87
2-4 years	100-142	73-87
4-13 years	110-155	73-95
Boys 13-17 years	130-160	76-98
Girls 13-17 years	125-160	78-102

Supplementary Table 2. Baseline characteristics of 251 anemic children who received or did not receive diagnoses after their first gastrointestinal endoscopies.

	Diagnosis N=183		No diagnosis N=68		P value
Categorical variables	N	**%**	N	**%**	
Girls	95	51.9	40	58.8	0.329
Autoimmune disease[1]	14	7.7	6	8.8	0.760
Asthma, allergy or atopy	34	18.6	10	14.7	0.473
Other chronic disease	22	12.0	10	14.7	0.571
Intestinal disease in relatives[2]	38	20.8	10	14.7	0.278
Positive EmA or TGA-IgA	67[3]	48.9	3[3]	7.5	<0.001*
Fecal calprotectin > 100µg/g	60[4]	81.1	5[4]	25.0	<0.001*
Low MCV	74[5]	45.7	17[5]	32.1	0.082
Continuous variables	No. of data	Median (quartiles)	No. of data	Median (quartiles)	
Age, years, (range)	183	10.8 (0.03, 16.4)	68	9.8 (0.04, 16.7)	0.757
ESR, mm/hr	121	16.0 (7.0, 28.5)	47	8.0 (3.0, 15.0)	0.002*
Alanine aminotransferase, U/l	133	18.0 (13.0, 28.5)	39	21.0 (14.0, 31.0)	0.236
Albumin, g/l	81	35 (33, 39)	21	39 (37, 42)	0.008*

[1]Type 1 diabetes, rheumatic or thyroidal disease, celiac disease; [2]Celiac disease or inflammatory bowel disease; [3]Data from 137 diagnosed and 40 non-diagnosed patients; [4]Data from 74 diagnosed and 20 non-diagnosed patients; [5]Data from 162 diagnosed and 53 non-diagnosed patients; [*]P-value≤0.050; EmA, anti-endomysial antibodies; ESR, erythrocyte sedimentation rate; MCV, mean corpuscular volume; TGA-IgA, IgA-antibodies against transglutaminase 2.

Supplementary Table 3. Relationships between symptoms and diagnosis adjusted for presence of anemia in 251 children with and 613 without anemia.

	Odds ratio[1] for the diagnosis	95% CI	P-value
Anemia	3.50	2.50-4.91	<0.001*
Abdominal pain	0.91	0.67-1.23	0.539
Diarrhea	0.85	0.62-1.16	0.302
Melena/hematochezia	2.51	1.53-4.14	<0.001*
Poor weight gain/growth	3.24	1.69-6.20	<0.001*
Constipation	0.74	0.49-1.10	0.137
Vomiting	0.92	0.59-1.45	0.302
Reflux	0.78	0.50-1.21	0.270
Other[2]	0.82	0.61-1.10	0.177

[1]Calculated by multivariate binary regression analysis with 95% confidence intervals (CI); [2]Other symptoms included e.g. fatigue, persistent fever, and dermatological symptoms; *P-value≤0.050.

Supplementary Table 4. Characteristics of 30 children who had anemia without gastrointestinal symptoms and received or did not receive diagnoses after their first gastrointestinal endoscopies.

	Diagnosis N=22		No diagnosis N=8		P value
Categorical variables	N	**%**	N	**%**	
Girls	15	68.2	3	37.5	0.210
Autoimmune disease[1]	3	13.6	1	12.5	1.000
Asthma, allergy or atopy	3	13.6	0	0	0.545
Other chronic disease	3	13.6	1	12.5	1.000
Intestinal disease in relatives[2]	2	9.1	1	12.5	1.000
Positive EmA or TGA-IgA	13[3]	72.2	0[3]	0	0.007*
Fecal calprotectin > 100µg/g	5[4]	100	1[4]	33.3	0.107
Low MCV	12[5]	75.0	3[5]	50.0	<0.001*
Continuous variables	No. of data	Median (quartiles)	No. of data	Median (quartiles)	
Age, years, (range)	22	9.4 (1.4, 15.3)	8	12.3 (0.04, 15.1)	0.963
ESR, mm/hr	9	12.0 (5.5, 21.0)	5	5.0 (3.0, 16.5)	0.180
Alanine aminotransferase, U/l	11	22.0 (17.0, 29.0)	5	17.0 (11.0, 81.5)	0.609
Albumin, g/l	7	28.0 (32.0, 42.0)	2	31.5 (21.00, -)	0.766

[1]Type 1 diabetes, rheumatic or thyroidal disease, celiac disease; [2]Celiac disease or inflammatory bowel disease; [3]Data from 18 diagnosed and five non-diagnosed patients; [4]Data from five diagnosed and three non-diagnosed patients; [5]Data from 16 diagnosed and six non-diagnosed patients; *P-value≤0.050; EmA, anti-endomysial antibodies; ESR, erythrocyte sedimentation rate; MCV, mean corpuscular volume; TGA-IgA, IgA-antibodies against transglutaminase 2.

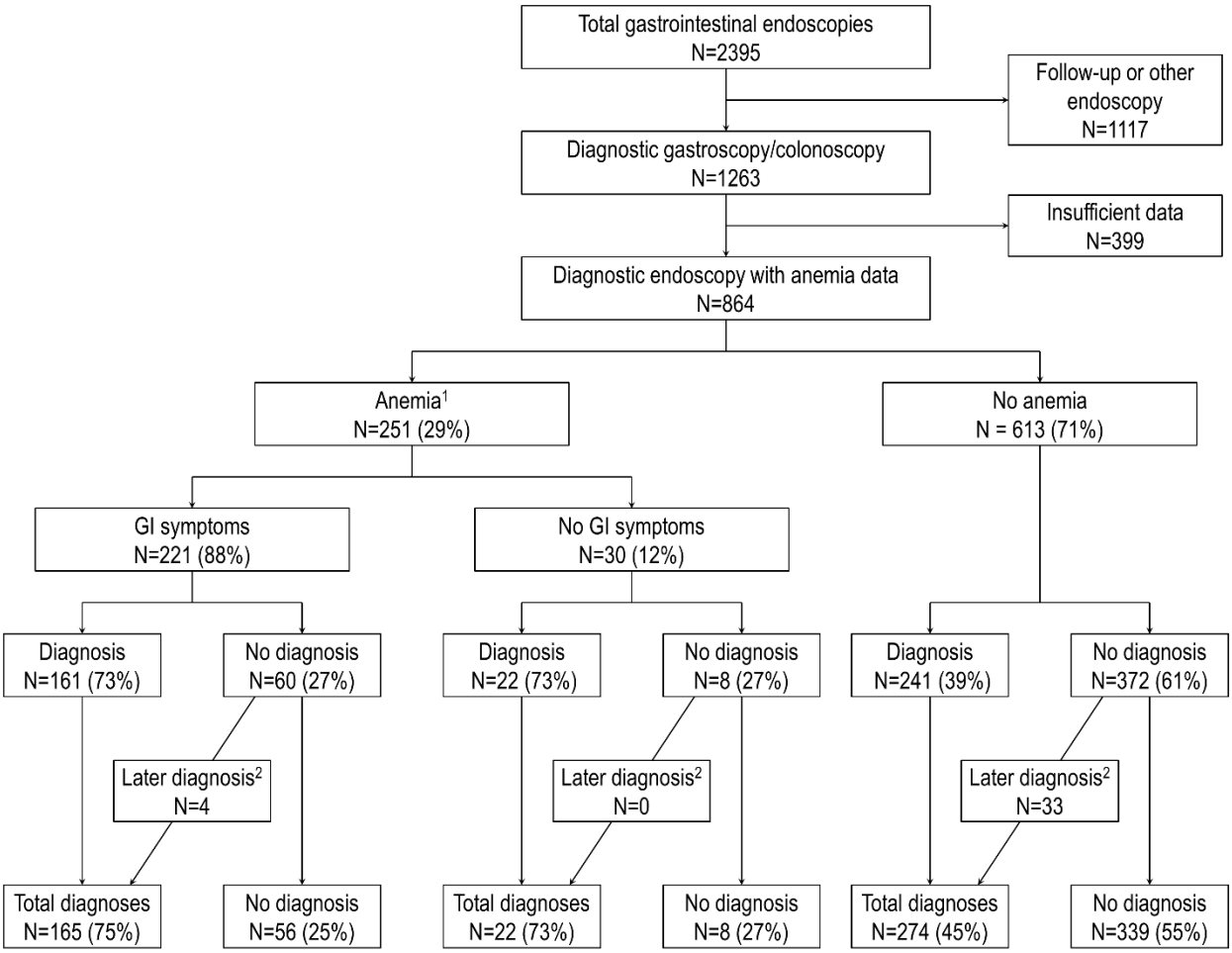
Total gastrointestinal endoscopies
N=2395
Follow-up or other endoscopy
N=1117
Diagnostic gastroscopy/colonoscopy
N=1263
Insufficient data
N=399
Diagnostic endoscopy with anemia data
N=864
Anemia[1]
N=251 (29%)
No anemia
N = 613 (71%)
GI symptoms
N=221 (88%)
No GI symptoms
N=30 (12%)
Diagnosis
N=161 (73%)
No diagnosis
N=60 (27%)
Diagnosis
N=22 (73%)
No diagnosis
N=8 (27%)
Diagnosis
N=241 (39%)
No diagnosis
N=372 (61%)
Later diagnosis[2]
N=4
Later diagnosis[2]
N=0
Later diagnosis[2]
N=33
Total diagnoses
N=165 (75%)
No diagnosis
N=56 (25%)
Total diagnoses
N=22 (73%)
No diagnosis
N=8 (27%)
Total diagnoses
N=274 (45%)
No diagnosis
N=339 (55%)

Figure 1.

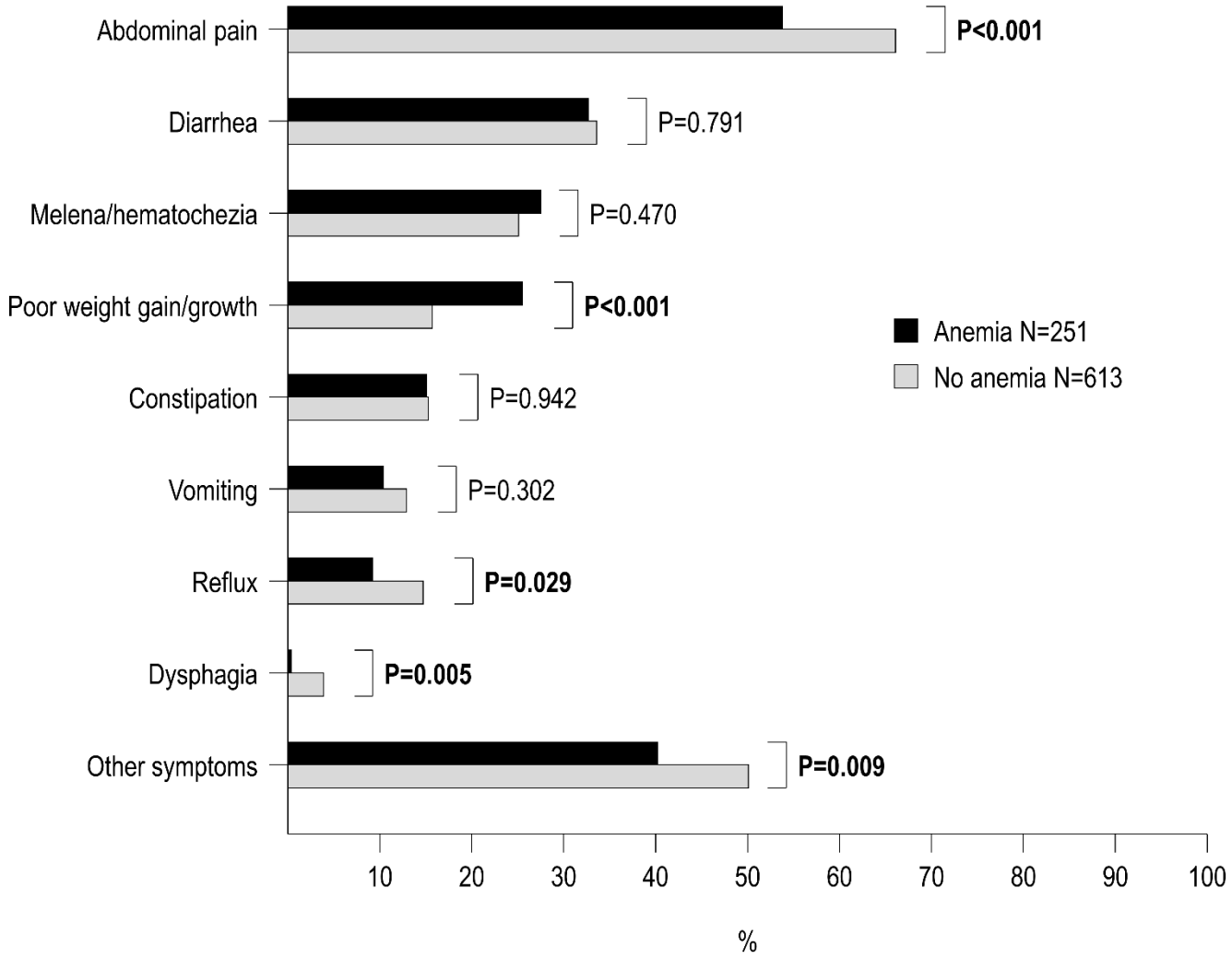
Abdominal pain
Diarrhea
Melena/hematochezia
Poor weight gain/growth
Constipation
Vomiting
Reflux
Dysphagia
Other symptoms
P<0.001
P=0.791
P=0.470
P<0.001
P=0.942
P=0.302
P=0.029
P=0.005
P=0.009
Anemia N=251
No anemia N=613
10
20
30
40
50
60
70
80
90
100
%

Figure 2.

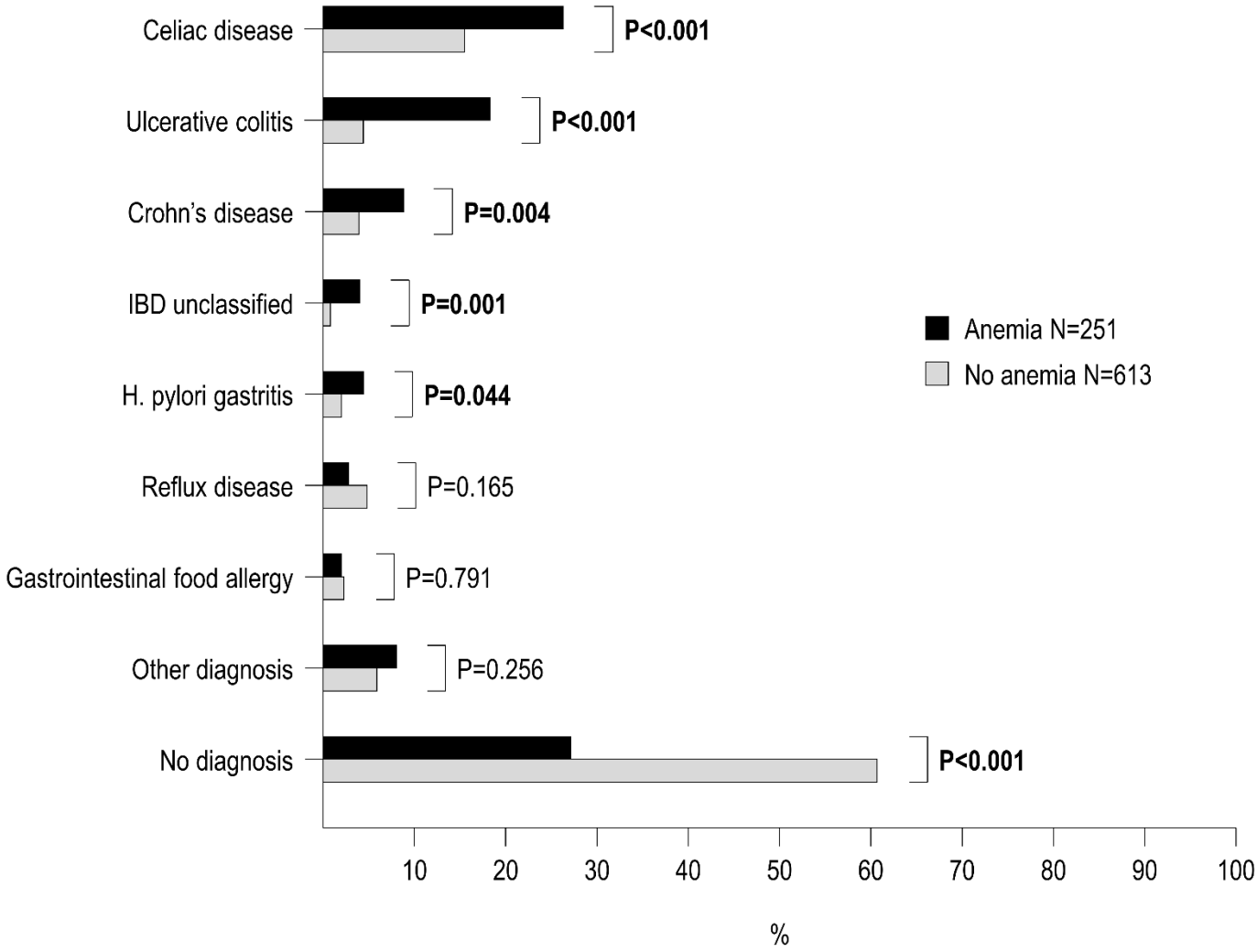
Celiac disease
P<0.001
Ulcerative colitis
P<0.001
Crohn's disease
P=0.004
IBD unclassified
P=0.001
H. pylori gastritis
P=0.044
Reflux disease
P=0.165
Gastrointestinal food allergy
P=0.791
Other diagnosis
P=0.256
No diagnosis
P<0.001
Anemia N=251
No anemia N=613
10
20
30
40
50
60
70
80
90
100
%

Figure 3.