Disease Phenotype at Diagnosis in Pediatric Crohn's Disease: 5-year Analyses of the EUROKIDS Registry

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Background: It has been speculated that pediatric Crohn's disease (CD) is a distinct disease entity, with probably different disease subtypes. We therefore aimed to accurately phenotype newly diagnosed pediatric CD by using the pediatric modification of the Montreal classification, the Paris classification.

Methods: Information was collected from the EUROKIDS registry, a prospective, web-based registry of new-onset pediatric IBD patients in 17 European countries and Israel. When a complete diagnostic workup was performed (ileocolonoscopy, upper gastrointestinal [GI] endoscopy, small bowel imaging), CD patients were evaluated for ileocolonic disease extent, esophagogastroduodenal involvement, and jejunal/proximal ileal involvement. Disease behavior and the occurrence of granulomas were also analyzed.

Results: In all, 582 pediatric CD patients could be classified according to the Paris classification. Isolated terminal ileal disease (±limited cecal disease) was seen at presentation in 16%, isolated colonic disease in 27%, ileocolonic disease in 53%, and isolated upper GI disease in 4% of patients. In total, 30% had esophagogastroduodenal involvement and 24% jejunal/proximal ileal disease. Patients with L2 disease were less likely to have esophagogastroduodenal involvement or stricturing disease than patients with L1 or L3 disease. Terminal ileal disease and stricturing disease behavior were more common in children diagnosed after 10 years of age than in younger patients. Granulomas were identified in 43% of patients.

Conclusions: Accurate phenotyping is essential in pediatric CD, as this affects the management of individual patients. Disease phenotypes differ according to age at disease onset. The Paris classification is a useful tool to capture the variety of phenotypic characteristics of pediatric CD.

(Inflamm Bowel Dis 2012;000:000–000)

Key Words: Crohn's disease, pediatrics, Paris classification, disease phenotype, granulomas

Inflammatory bowel diseases (IBD), such as Crohn's disease (CD) and ulcerative colitis (UC), are an increasing health concern and medical burden for the Western, and particularly European and North American, countries affecting up to 1 in 250 individuals in the general population.[1] Every fourth patient with IBD is diagnosed during childhood and adolescence. After a continuous rise in the incidence of adult CD over the last five decades, several recent studies have shown that the rates reached a stable plateau.[2–5] In contrast to adults, incidence rates for children continue to rise,[5–12] especially in children <10 years of age.[13]

There is a striking variety of pediatric-onset IBD regarding age, disease distribution and severity at onset, endoscopic appearance, histology, genetic background, serologic markers, comorbidities, complications during follow-up, and response to different treatment options. Up to now, no single diagnostic procedure or even a combination of diagnostic tests allows the definite diagnosis of CD. It has been speculated that pediatric CD is a distinct disease entity, with probably different disease subtypes.[14] The recent pediatric modification of the Montreal classification for IBD could facilitate future studies and help to further explore this hypothesis, as it enables a more precise phenotypic classification of disease location.[15] The European multicenter 5-years recruitment of children with newly developed IBD (EUROKIDS registry) provides a unique opportunity to test this hypothesis, as the majority of

Received for publication March 12, 2012; Accepted April 11, 2012.

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The EUROKIDS project received financial support from ESPGHAN.

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DOI 10.1002/ibd.23008

Published online in Wiley Online Library (wileyonlinelibrary.com).

included patients have undergone a complete diagnostic workup suggested by the so-called Porto criteria.[16]

The aim of this study was to accurately phenotype newly diagnosed CD in pediatric patients prospectively recruited within the EUROKIDS registry with respect to: disease location, disease behavior, and presence of granulomas. Associations between phenotype and age at disease-onset, gender, family history of IBD, ethnicity, geographical region, and extraintestinal involvement were also investigated.

MATERIALS AND METHODS

EUROKIDS Registry

The EUROKIDS registry is a prospective, web-based registry of newly diagnosed pediatric IBD patients in Europe and Israel, established by the IBD Working Group of the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN). The enrolment of patients into the registry began in May 2004. During the first 5 years, the registry has been extended to allow inclusion of patients (aged 0–18 years) from 44 centers in 18 countries. Details on the establishment of the registry and data collection have been previously reported.[17]

Participating centers were all committed to perform a diagnostic workup of their patients (who were suspected of having IBD) according to the Porto criteria.[16] This implies that ileocolonoscopy and upper gastrointestinal (GI) endoscopy were expected to be performed in all patients, as well as imaging of the small bowel (except in patients with a definitive diagnosis of UC). Also according to the agreed Porto criteria, participating centers were expected to take at least two biopsies from each segment of the GI tract (esophagus, stomach, duodenum, terminal ileum, and all segments of the colon), and to register the endoscopic and histologic findings from each segment separately. Each segment visualized by ileocolonoscopy could be registered as macroscopically "normal" or "abnormal" (i.e., abnormalities consistent with IBD, such as (aphthous) ulcerations, erosions, cobblestoning, strictures). Histology was classified as "normal" or "abnormal" in the first year of the registry (May 2004 to April 2005), while the presence or absence of granulomas could be registered from May 2005 onward (second year of the registry). The number of biopsies taken from each segment was not registered in the database. Results from upper GI endoscopy were reported in a similar fashion. Macroscopic esophagogastroduodenal findings were classified as "normal" or "abnormal" in the first 3 years of the registry (i.e., May 2004 to April 2007), whereas additional information on the type of macroscopic abnormality was registered in years 4 and 5 only (i.e., May 2007 to April 2009). To have more specific information on the "abnormal" esophagogastroduodenal findings in pediatric CD patients, participating centers were asked to review the medical charts of these patients for additional information on the type of macroscopic abnormality in the upper GI tract. Results from small bowel imaging ("normal" or "abnormal") were also registered per segment of the GI tract.

Ethics Committee permission was obtained in the United Kingdom, Sweden, and Poland. In all other countries a Statement of No Objection was released by the local Ethics Committees because data were anonymously collected.

Eligibility

As previously described,[17] 2087 newly diagnosed pediatric IBD patients who were diagnosed between May 2004 and April 2009 were correctly registered in the database. For this study we identified all patients who were classified as having CD. Exclusion criteria were: a diagnosis of UC or IBD-unclassified, missing information on ileocolonoscopy and ileocolonic histology, and a diagnostic workup without endoscopic, histologic, and radiologic abnormalities.

Definitions

A diagnosis of CD was made according to the discretion of the investigator/treating physician, and was based on clinical presentation, physical examination, endoscopic appearance, histologic findings, and small bowel imaging studies.

Participating countries were divided into two geographical regions: Northern Europe (Belgium, Czech Republic, Denmark, France, Germany, Latvia, the Netherlands, Norway, Poland, Sweden, United Kingdom) and Southern Europe and Israel (Croatia, Greece, Hungary, Italy, Portugal, Slovenia). Family history of IBD was defined as the presence of IBD in first-degree relatives.

Extraintestinal manifestations (including dermatologic, ophthalmologic, musculoskeletal, and/or hepatobiliary manifestations) were registered as being present or absent. Registration of the type of manifestation was optional.

To optimally classify disease location, we decided to select the pediatric CD patients who had a complete diagnostic workup according to the Porto criteria.[16] This workup had to consist of upper GI endoscopy, ileocolonoscopy, and adequate imaging of the small bowel by small bowel follow-through (SBFT), magnetic resonance imaging (MRI), computed tomography (CT), capsule endoscopy, and/or enteroscopy. Disease location was determined by the endoscopic appearance of the mucosa and radiologic involvement of the small bowel, not by microscopic findings. Endoscopic information on the terminal ileum was considered more accurate than radiologic findings, in case of disagreement. Disease location was categorized according to the Paris classification[15]: (L1) involvement of the terminal ileum only, with limited or no cecal disease; (L2) colonic involvement only; (L3) involvement of both the terminal ileum and colon; (L4) isolated upper GI disease, defined as macroscopic and/or radiologic abnormalities proximal to the terminal ileum. Isolated upper GI disease (L4) was further separated into esophagogastroduodenal disease (L4A), jejunal/proximal ileal disease (L4B), or both L4A and L4B. Upper GI disease (i.e., L4A, L4B, L4AB) can also coexist

with L1, L2, or L3. We defined esophagogastroduodenal disease (L4A) as the presence of ulcerations, erosions/aphthae, cobblestones, and/or stenosis. The presence of mucosal erythema, edema, granularity, and/or nodularity was not sufficient to be considered evidence of involvement.

Disease behavior was registered as the presence of strictures, intraabdominal fistulas, and/or intraabdominal abscesses. We categorized disease behavior according to the Paris classification[15]: (B1) nonstricturing, nonpenetrating disease; (B2) stricturing disease; (B3) penetrating disease (excluding isolated perianal or rectovaginal fistulas); (B2B3) the presence of both B2 and B3 phenotypes in the same patient.

Perianal disease was defined as the presence of a perianal abscess and/or fistula, and did not include the isolated presence of skin tags, fissures, or hemorrhoids.

Histology was registered as "normal," "abnormal," or "granulomas" from May 2005 onward (i.e., the second year of the registry). As details on the histologic abnormalities (i.e., other than granulomas) were not available, we only used data on the presence of granulomas. For these analyses we selected the patients diagnosed from May 2005 onward who had biopsies from at least 10 segments of the GI tract, including the esophagus, stomach, duodenum, terminal ileum, cecum, ascending colon, transverse colon, descending colon, sigmoid, and rectum. Information on the number of granulomas found was not available.

Statistical Analysis

Data were analyzed in SPSS (v. 17.0, Chicago, IL). Descriptive statistics were calculated as percentages for discrete data. Continuous variables were presented as means and standard deviations (SD). Age at diagnosis was dichotomized into two categories (<10 years, ≥10 years), in accordance with the age cutoffs recommended in the Paris classification.[15] To test for differences between more than two categories of disease location or disease behavior, we used Pearson χ^2 tests. Two-sample *t*-tests were used to compare two continuous variables, while Fisher's exact tests were used to compare two proportions. Multivariate logistic regression was performed to examine the possible independent determinants of the occurrence of granulomas after adjusting for gender, age (<10 years, ≥10 years), family history of IBD, ethnicity, and geographical region. Statistical significance was defined as a two-tailed $P < 0.05$.

RESULTS

Patient Characteristics

Between May 2004 and April 2009, 1227 of 2087 (59%) newly diagnosed pediatric IBD patients were classified as having CD. Six patients (0.5%) were excluded because of missing information on ileocolonoscopy and histology ($n = 4$), and a diagnostic workup without endoscopic, histologic, and radiologic abnormalities ($n = 2$).

In the remaining 1221 patients, mean age at diagnosis was 12.5 years (±3.3; range 0.8–17.9; 20% younger than 10 years), with 59% ($n = 723$) being male. The majority of patients (77%, $n = 936$) were from Northern Europe. Information on ethnicity was available in 1210 (99%) patients. Most patients were Caucasian (87%, $n = 1049$), 4% ($n = 50$) were Asian, 4% ($n = 43$) of Arab origin, 1% ($n = 18$) of Africa-Caribbean origin, and 4% ($n = 50$) had another ethnicity. Eleven percent (129/1193) of patients had a first-degree relative with IBD. When analyzed by age category (<10 years, ≥10 years), there was no significant difference in the prevalence of a positive family history in first-degree relatives ($P = 0.82$). Extraintestinal manifestations were present in 20% (231/1178) of patients at diagnosis.

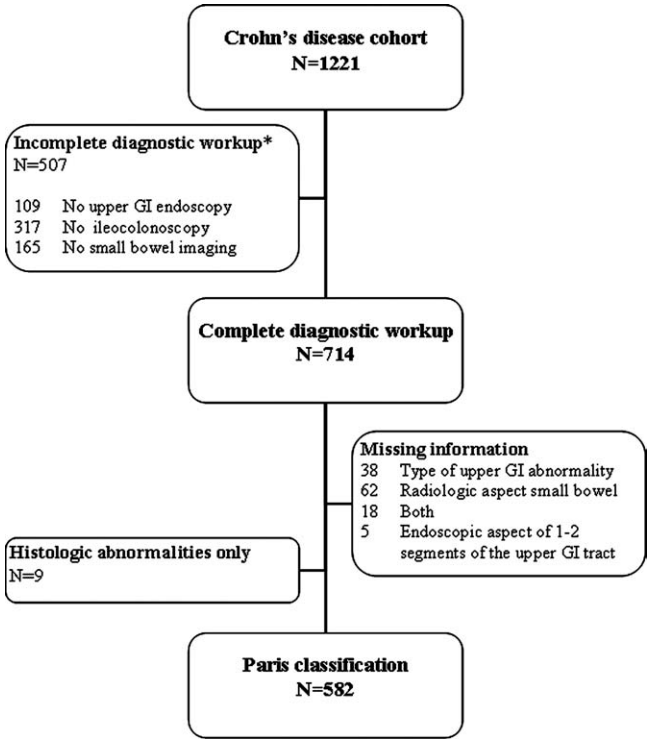

FIGURE 1. Flowchart of CD patients selected for the analyses on disease location according to the Paris classification. *Multiple diagnostic tests can be absent in one patient simultaneously. GI: gastrointestinal.

Disease Location According to the Paris Classification

A total of 582 CD patients (48%) were eligible for determination of disease location according to the Paris classification (Fig. 1). Isolated terminal ileal disease (±limited cecal disease, L1) was seen at presentation in 16% ($n = 95$), isolated colonic disease (L2) in 27% ($n = 159$), ileocolonic disease (L3) in 53% ($n = 307$), and isolated upper GI disease (L4) in 4% ($n = 21$) of pediatric CD patients (Fig. 2).

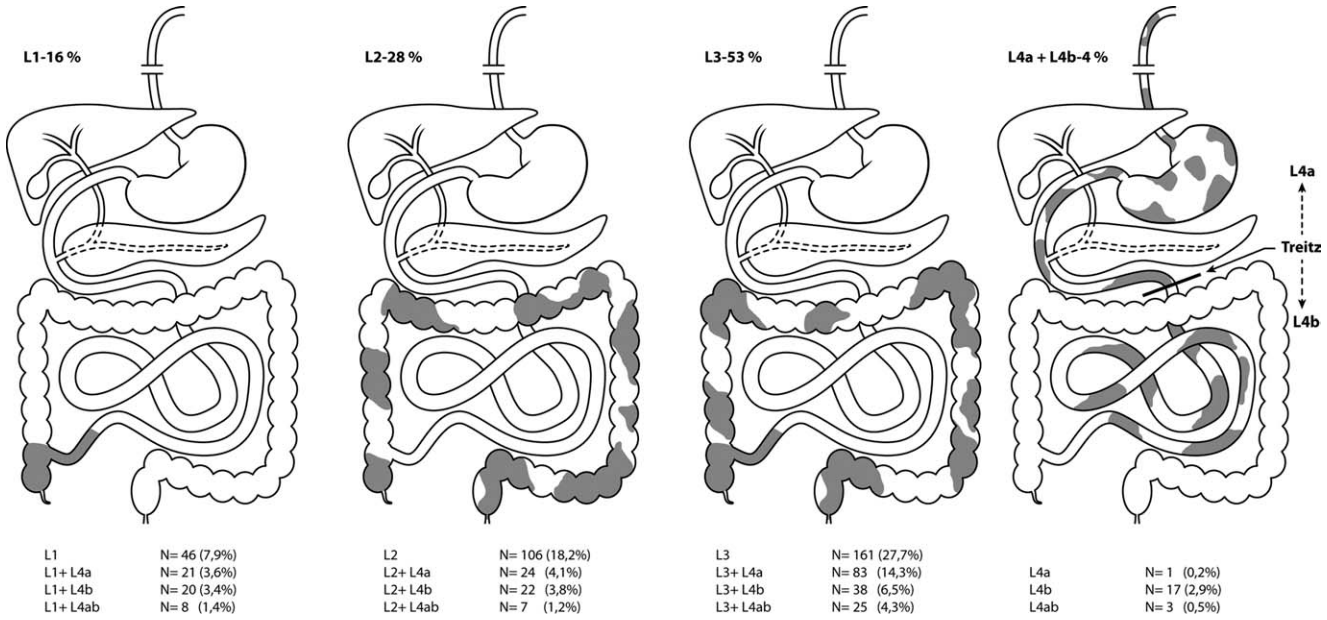

FIGURE 2. Disease location according to the Paris classification in 582 newly diagnosed pediatric CD patients who underwent a complete diagnostic workup according to the Porto criteria.[16] L1: terminal ileal disease (±limited cecal disease). L2: colonic disease. L3: ileocolonic disease. L4: isolated upper gastrointestinal tract disease. L4A: esophagogastroduodenal disease. L4B: jejunal/proximal ileal disease.

Differences in disease location according to age at diagnosis are shown in Figure 3. Isolated colonic disease was recorded in 41% (47/114) of children diagnosed before 10 years of age compared with 24% (111/467) of older children ($P < 0.001$). Consequently, the proportion of patients diagnosed with L1 disease (9% vs. 18%, $P = 0.016$) and, to a lesser extent, L3 disease (47% vs. 54%, $P = 0.14$) were lower in the younger age category. There was no difference in the occurrence of L4 disease between the two age categories (both 4%). Gender, family history of IBD, or presence of extraintestinal manifestations did not differ significantly between the four disease locations. L4 disease was more often diagnosed in Southern Europe and Israel than in Northern Europe (7.3% vs. 2.2%, $P = 0.005$), whereas the occurrence of the other three disease locations did not differ according to geographical region. Ethnicity differed significantly between the four disease locations, as L3 disease occurred more often in Caucasian patients (55% vs. 38%, $P = 0.016$). Consequently, L1 disease (25% vs. 15%, $P = 0.048$) and L4 disease (13% vs. 3%, $P = 0.001$) were more often present in non-Caucasian patients.

Esophagogastroduodenal disease (L4A) was present in 30% ($n = 172$) of pediatric CD patients at disease onset. The distribution of the macroscopic findings in the upper GI tract is displayed in Table 1. In the majority of patients with L4A disease (68%, 117/172), the mucosal abnormalities were limited to one upper GI segment, preferentially the stomach ($n = 54$) or duodenum ($n = 49$). L4A disease occurred more often in patients with L1 or L3 disease than in those with L2 disease (31% vs. 35% vs. 20%, $P = 0.002$, Table 2). There were no significant differences between patients with and without L4A disease according to age category, gender, family history of IBD, geographical region, ethnicity, presence of extraintestinal manifestations, or L4B disease.

Jejunal/proximal ileal disease (L4B) was present in 24% ($n = 140$) of pediatric CD patients. L4B disease occurred more often in patients with L1 disease than in those with L2 or L3 disease (30% vs. 18% vs. 21%, $P = 0.092$, Table 2). The presence of L4B disease was not related to age, gender, family history of IBD, geographical region, or presence of extraintestinal manifestations. Caucasian patients

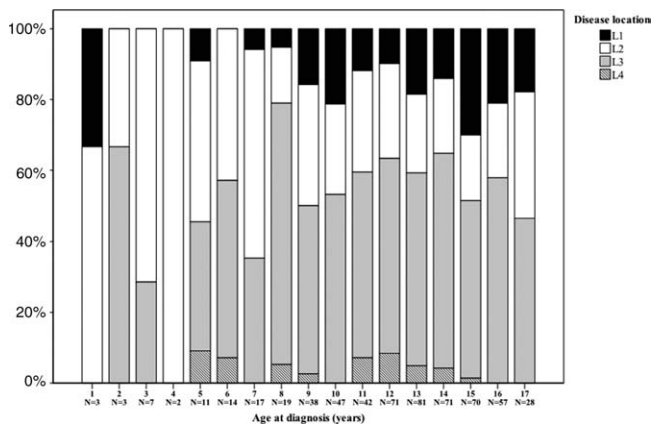

FIGURE 3. Disease location in newly diagnosed pediatric CD patients according to age at diagnosis. L1: terminal ileal disease (±limited cecal disease). L2: colonic disease. L3: ileocolonic disease. L4: isolated upper gastrointestinal tract disease.

TABLE 1. Macroscopic Findings in the Upper Gastrointestinal Tract of 582 Pediatric Crohn's Disease Patients Who Underwent a Complete Diagnostic Workup According to the Porto Criteria[16]

Esophageal involvement	34 (6%)
Ulcerations	12
Erosions/aphthae	23
Gastric involvement	102 (18%)
Ulcerations	36
Erosions/aphthae	71
Cobblestones	1
Duodenal involvement	100 (17%)
Ulcerations	31
Erosions/aphthae	72
Cobblestones	2
Stenosis	2

Multiple abnormalities may be present in one segment simultaneously.

were less likely to have disease involvement of the jejunum and/or proximal ileum than Non-Caucasian patients (22% vs. 41%, $P = 0.002$). L4B disease was present in 47% (9/19) of Asian patients, 22% (4/18) of patients of Arab origin, 75% (3/4) of patients of Africa-Caribbean origin, and 46% (10/22) of patients with another ethnicity.

Disease Behavior

Information on disease behavior was available in 1177 (96%) patients. The majority of pediatric CD patients (82%, $n = 959$) presented with nonstricturing, nonpenetrating disease (B1), while stricturing disease (B2) was seen in 12% ($n = 144$), penetrating disease (B3) in 5% ($n = 55$), and both stricturing and penetrating disease (B2B3) in 2% ($n = 19$) of patients at initial diagnosis. Patients diagnosed before 10 years of age were more likely to present with B1 disease compared with older children (88% [208/236] vs. 80% [750/940], $P = 0.003$). Consequently, the proportion of patients with B2 disease (7% [16/236] vs. 14% [128/940], $P = 0.004$) and B2B3 disease (0.4% [1/236] vs. 2% [18/940], $P = 0.15$) were lower in the younger age category. The occurrence of B3 disease did not differ between the two age categories (both 5%). Disease behavior was not related to gender, family history of IBD, geographical region, ethnicity, or presence of extraintestinal manifestations.

Perianal disease (i.e., presence of fistula(s) and/or abscess(es)) at diagnosis was seen in 9% (114/1207) of pediatric CD patients. Male patients were more likely to have perianal disease than female patients (12% vs. 6%, $P = 0.002$). There was no significant association with age at diagnosis, family history of IBD, geographical region, ethnicity, or presence of extraintestinal manifestations. Presence of perianal disease differed significantly between the four disease behavior categories ($P < 0.001$). Perianal disease occurred more often in patients with B3 disease than in patients with B1 disease (38% vs. 8%, $P < 0.001$), B2 disease (38% vs. 7%, $P < 0.001$), or B2B3 disease (38% vs. 17%, $P = 0.15$).

Table 2 displays the associations between disease location and disease behavior in the 582 pediatric CD patients who could be classified according to the Paris classification. Patients with L2 disease were less likely to have stricturing disease complications compared with patients with L1 or L3 disease (6% vs. 21% vs. 15%, $P = 0.005$). The occurrence of penetrating disease behavior did not differ significantly between the four disease locations, nor were there significant differences in disease behavior between patients with or without L4A/L4B disease.

Granulomas

In years 2 to 5, there were 427 pediatric CD patients with biopsies from at least 10 segments of the GI tract.

TABLE 2. Associations Between Ileocolonic Disease Location and Upper Gastrointestinal Disease, Disease Behavior, and Perianal Disease in 582 Pediatric Crohn's Disease Patients Who Underwent a Complete Diagnostic Workup According to the Porto Criteria[16]

	Disease Location According to the Paris Classification				
	L1	L2	L3	L4	P[a]
L4A	29/95 (31%)[b]	31/159 (20%)	108/307 (35%)[b]	NA	0.002
L4B	28/95 (30%)[b]	29/159 (18%)	63/307 (21%)	NA	0.092
Stricturing disease behavior	20/95 (21%)[b]	9/155 (6%)	45/306 (15%)[b]	3/21 (14%)	0.005
Penetrating disease behavior	5/94 (5%)	6/153 (4%)	17/302 (6%)	0/21 (0%)	0.62
Perianal disease	2/95 (2%)[c]	13/156 (8%)	32/305 (11%)	1/21 (5%)	0.070

[a]L1 vs. L2 vs. L3 (vs. L4), Pearson χ^2.
[b]$P < 0.05$ vs. L2.
[c]$P < 0.05$ vs. L3.
L1: terminal ileal disease (± limited cecal disease). L2: colonic disease. L3: ileocolonic disease. L4: upper gastrointestinal tract disease. L4A: esophagogastroduodenal disease. L4B: jejunal/proximal ileal disease. NA: not applicable.

TABLE 3. Distribution of Granulomas in the Gastrointestinal Tract of 427 Pediatric Crohn's Disease Patients at Diagnosis Who Had Biopsies of at Least 10 Segments of the Gastrointestinal Tract, Including the Esophagus, Stomach, Duodenum, Terminal Ileum, Cecum, Ascending Colon, Transverse Colon, Descending Colon, Sigmoid, and Rectum

Biopsy Site	Presence of Granulomas
Esophagus	20 (5%)
Normal macroscopic appearance	13
Stomach	49 (12%)
Normal macroscopic appearance	27
Duodenum	14 (3%)
Normal macroscopic appearance	5
Terminal ileum	86 (20%)
Normal macroscopic appearance	23
Colon	141 (33%)
Normal macroscopic appearance	31

Granulomas may be present in biopsies from multiple sites simultaneously.

Granulomas were identified in 43% (184/427) of these patients. The distribution of granulomas per segment of the GI tract is represented in Table 3. In 79 CD patients (19%), granulomas were found in one or more macroscopically normal-looking segments.

Granulomas confined solely to the upper GI tract were present in 4% (18/427), granulomas confined solely to the terminal ileum in 5% (21/427), and granulomas confined solely to the colon in 15% of CD patients (65/427). Eight percent of patients (32/427) had granulomas in the upper GI tract, as well as in the terminal ileum and colon.

There was no significant age difference between CD patients with and without granulomas (12.4 vs. 12.2 years, $P = 0.57$). In addition, the presence of granulomas was not related to gender, family history of IBD, geographical region, ethnicity, presence of extraintestinal manifestations, esophagogastroduodenal disease, jejunal/proximal ileal disease, perianal disease, stricturing disease behavior, or penetrating disease behavior. Subsequent multivariate analyses revealed no other significant determinants of granulomas.

DISCUSSION

This is one of the largest European studies so far describing disease phenotype at diagnosis in pediatric CD patients. Data from 17 European countries and Israel were included in the EUROKIDS registry in a prospective manner, based on clearly defined diagnostic criteria. Among 2087 children with IBD, 1227 (59%) were classified as having CD, which is in accordance with other pediatric publications that predominantly report CD to be more common than UC.[18] Extraintestinal manifestations occurring in 20% and perianal disease in 9% of patients are also in line with other recent pediatric reports.[14,19–21]

We were able to stratify macroscopic disease location according to the Paris classification for pediatric IBD[15] in 582 patients with a complete workup according to the Porto criteria.[16] Little more than half of the patients presented with ileocolonic disease, which is in keeping with recent pediatric reports based on the Montreal classification.[14,19] Our data also confirm that disease location is clearly dependent on the age of disease onset, with younger children having a tendency to isolated colonic disease and older children having a more frequent involvement of the terminal ileum. Clinical observations have suggested that the sites of initial inflammation in ileal CD are the lymphoid follicles and Peyer's patches.[22] The number of Peyer's patches increases during childhood and reaches a peak in late adolescence,[23] which is highly correlated with the age-related occurrence of CD. French data have confirmed the importance of ileal maturation and thus function of Peyer's patches,[24,25] which might be an explanation for the association between age and disease location.

The Paris classification enables a more detailed phenotypic description of upper GI disease than the Montreal classification,[26] thereby adding new information about the phenotype of childhood IBD to the pediatric literature. Using a stringent definition for esophagogastroduodenal disease (L4A) based on macroscopic criteria, we found that 30% of patients presented with ulcerations, erosions/aphthae, cobblestones, and/or stenosis in the upper GI tract. When we had defined L4A disease as the presence of ulcerations only, the prevalence would have been 11%. In previous pediatric cohort studies, esophagogastroduodenal disease has been variably defined by macroscopic and/or histologic definitions, resulting in a large range of reported frequencies varying from 11%–52%.[14,19,27–29] Future studies should use clear definitions for esophagogastroduodenal disease in order to determine the effect of this phenotype on the disease course. Jejunal/proximal ileal disease (L4B) was present in 24% of patients, which is slightly higher compared with rates reported in other studies (19 and 17%, respectively).[29,30] Our increased detection rate of L4B involvement may be explained by the technologic advances in radiologic imaging techniques in recent years. In total, 64% (373/582) of pediatric CD patients underwent small bowel follow-through, 38% (218/582) MRI, 6% (37/582) CT abdomen, and 5% (29/582) capsule endoscopy. Previous studies have demonstrated that patients with the L4B phenotype were more likely to be stunted at diagnosis[29,30] and develop early complications, particularly of the stricturing type.[31,32] Early diagnosis of proximal small bowel disease is therefore important, as this may allow physicians

to treat these patients more aggressively in order to improve linear growth and prevent complications.

Disease behavior was classified as inflammatory (nonstricturing, nonpenetrating; B1: 82%), stricturing (B2: 12%), penetrating (B3: 5%), or both stricturing and penetrating (B2B3: 2%). In comparison, two other recently published pediatric cohort studies from Europe found the B1, B2, and B3 phenotype at diagnosis in 92, 4, and 4%, and 71, 25, and 4%, respectively.[14,19] The large differences in reported frequencies of the B2 phenotype may reflect difficulties in precise discrimination of fibrostenotic from inflammatory stenotic disease. Our study showed that disease behavior differed with respect to age at diagnosis, as older patients had a higher risk of stricturing disease. Previous studies have yielded conflicting results regarding the influence of age on disease behavior. Gupta et al[33] demonstrated that older children with CD had an increased risk of developing strictures, but also of developing abscesses or fistulas. In contrast, Shaoul et al[34] did not find an association between age and disease behavior. The association between age and disease behavior might be the effect of the influence of age on disease location, as older patients are more likely to have ileal disease, which in turn has been demonstrated to be associated with stricturing disease complications.[14] We also found an association between the occurrence of perianal disease and intraabdominal penetrating disease, similar to results from adult studies.[35,36] Although the two phenotypes are related to one another, perianal disease and intraabdominal penetrating disease have different clinical associations with disease location and smoking behavior.[36,37] This suggests that the mechanisms for these types of penetrating disease are at least partly different.

We found granulomas in 43% of patients who were biopsied in at least 10 segments of the GI tract, with isolated localization in the terminal ileum in 5%, and in the upper GI tract in 4%. This differs considerably from the study of De Matos et al,[38] who published the hitherto most detailed study regarding location of granulomas in pediatric CD. They found granulomas in 61% (112/184) of untreated patients, of which 23% had granulomas only in the terminal ileum and 13% only in the upper GI tract. This variation in occurrence of granulomas may reflect differences in patient populations (either due to geographical variation or selection bias) or methodology (number of biopsies taken, number of sections per paraffin block, number of high-power fields evaluated, and definition of granulomas). However, both studies underscore the potential usefulness of intubating the terminal ileum and performing upper GI endoscopy at the time of diagnosis of IBD. We recently estimated the diagnostic yield of ileoscopy and upper GI endoscopy in CD patients to be 13% and 7.5%, respectively (i.e., the presence of isolated granulomas, or the presence of macroscopic abnormalities in the terminal ileum/upper GI tract without other characteristics of CD).[17] Data from the literature regarding the usefulness of upper GI endoscopy in the diagnostic workup of pediatric IBD have recently been reviewed.[39] Diagnostic yields ranged between 7 and 24%. This topic has not been studied in adult IBD patients.

Our study has certain limitations. First of all, EUROKIDS is not a population-based registry, but a selection of centers and pediatric gastroenterologists with a special interest in IBD. This has probably resulted in some selection bias. However, ESPGHAN recommends that all children with a suspicion of IBD should be referred to a pediatric gastroenterologist for diagnostic workup.[16] Consequently, the majority of our participating centers diagnose and treat all pediatric IBD patients in their region; only five centers have reported that they treat only the most severe IBD cases and four centers have a mixed population of "regular" IBD patients and severe IBD cases. Selection bias may also have been introduced due to our decision to include only CD patients with a complete workup according to the Porto criteria in the analyses on disease location according to the Paris classification, as patients with severe disease (risk of perforation, strictures) and younger patients (more difficult to reach the terminal ileum) are more prone not to have undergone a complete workup. However, age at diagnosis did not differ significantly between the included and excluded patients.

Another limitation is that the number of adolescents older than 14 years is underestimated in our study cohort. While it is generally known that the incidence of CD increases with age, the peak incidence in our study occurred at 14 years of age. This is a reflection of daily practice, where adolescents are often diagnosed by adult gastroenterologists, and are thus not included in our EUROKIDS registry. Approximately one-third of the participating centers reported that new patients older than 15 years are always referred to an adult gastroenterologist. Fourth, a clear definition for the occurrence of extraintestinal manifestations was lacking, which makes the incidence rate less reliable. However, our incidence is similar to rates reported in other large cohorts of newly diagnosed pediatric CD patients.[19,20,40] Other limitations are the risk of interobserver variation regarding interpretation of endoscopic and histologic findings, variation in number of biopsies taken at specific locations, and lack of data on follow-up to evaluate the correctness of the initial diagnosis.

In conclusion, our study applied the Paris classification in a large cohort of newly diagnosed pediatric CD patients, thereby providing detailed information on disease phenotype and confirming the results of previous studies on disease phenotype in newly diagnosed pediatric CD. During recent years pediatric IBD studies have improved in

quality and quantity due to more extensive use of multicenter collaborations and large databases, such as the US Pediatric IBD Consortium Registry,[33] the US/Canadian Pediatric IBD Collaborative Research Group Registry,[20,21] the EPIMAD registry of Northern France,[19] the Scottish cohort,[14] the Italian pediatric IBD registry,[28] the Danish Crohn Colitis Database,[11] and the German pediatric IBD registry CEDATA.[40] Increasingly, future pediatric IBD studies are likely to be the result of large registry collaborations more than single-center reports. Uniformity in disease classification will then be essential for assessing disease prognosis, choosing the most appropriate therapy, and investigating genotype–phenotype correlations.

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APPENDIX

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