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Addition of Histology to the Paris Classification of Pediatric Crohn's Disease Alters Classification of Disease Location

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Abstract

Objectives—To investigate the value of microscopic findings in the classification of Pediatric Crohn's Disease by determining whether classification of disease changes significantly with inclusion of histologic findings.

Methods—60 patients were randomly selected from a cohort of patients followed at the Pediatric Inflammatory Bowel Disease Clinic at the University of California San Francisco (UCSF) Benioff Children's Hospital San Francisco (BCHSF). Two physicians independently reviewed the electronic health records of the included cases to determine the Paris Classification for each patient by adhering to current guidelines and then by including microscopic findings.

Results—Macroscopic and combined disease location classification were discordant in 34 (56.6%), with no statistically significant differences between groups. Interobserver agreement was higher in the combined classification (kappa 0.7303, 95% Confidence Interval (C.I.) 0.650–0.821) as opposed to when classification was limited to macroscopic findings (kappa 0.5318, 95% C.I. 0.403–0.581). When evaluating the proximal upper gastrointestinal tract (Paris L4a) the interobserver agreement was better in macroscopic compared with the combined classification.

Conclusion—Disease extent classifications differed significantly when comparing isolated macroscopic findings (Paris Classification) with the combined scheme that included microscopy. Further studies are needed to determine which scheme provides more accurate representation of disease extent.

Keywords

Crohn's Disease; Phenotype; IBD

Introduction

The Paris classification(1), the pediatric modification to the Montreal classification(2), established standard definitions of pediatric IBD phenotypes. The Paris classification

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Conflicts of Interest:

The authors report no conflict of interest.

addressed nuances unique to pediatric IBD, in particular Crohn's disease, by distinguishing upper gastrointestinal tract locations and incorporating growth failure. However, disease location remained limited to macroscopic disease, a precedent established by adult classification schemes(2–5). The authors of the Montreal Classification addressed this limitation: "*The significance of histological evidence of chronic colitis in an endoscopically normal proximal colon* ***remains unclear*** *in terms of the risk of colectomy, cancer, proximal progression of the disease, or mortality*(2)." While the significance remains unclear, the need for a unique pediatric classification system demonstrates that childhood disease needs to be approached differently. Additionally, improvements in treatment options for IBD have led to changes in treatment goals and trial endpoints, with an almost universal target of achieving mucosal healing, optimally defined as endoscopic and histologic remission(6), thus supporting the inclusion of microscopic information when determining extent of disease.

To further investigate the value of microscopic findings, it is important to first establish if classification of disease changes significantly with inclusion of this information. We compared classifications of disease extent between the Paris classification with a modified scheme that combines macroscopic and microscopic disease findings.

Methods

Population

Eighty-eight cases were selected randomly from a cohort of patients followed at the Pediatric Inflammatory Bowel Disease Clinic at the University of California San Francisco (UCSF) Benioff Children's Hospital San Francisco (BCHSF). Patients were included if diagnosed with Crohn's disease before age 18, had at least one upper endoscopy and one colonoscopy that included ileal intubation performed at UCSF, and had no history of any intestinal resection prior to at least one endoscopy at UCSF. Sixty patient cases met specified criteria and were included in the study.

Study Design

Two physicians independently reviewed the electronic health records of the included cases to determine the (1) macroscopic disease location based on the Paris classification, and (2) the microscopic disease extent determined by pathology alone for each upper endoscopy and colonoscopy. Each reviewer had access to the electronic health record for all cases which included endoscopy procedure reports with associated pathology reports, radiology reports, and clinic notes. Microscopic disease extent was derived from reports written by attending pathologists at UCSF at the time of each endoscopy. Pathologists adhered to societal standards when composing the report. No cases were re-reviewed as part of this study. To determine the macroscopic disease extent based on the Paris classification, reviewers used information from endoscopy reports performed at UCSF and available radiology reports. Endoscopy reports were reviewed only if both an upper endoscopy and colonoscopy were performed and if an attending gastroenterologist finalized the procedure report. Per standard department practice, biopsies from colonoscopies are obtained from the ileum, cecum, ascending, transverse and descending and rectosigmoid colon and assessed separately. Biopsies are obtained from identified lesions and normal appearing mucosa at regular

intervals throughout the gastrointestinal tract. Abdominal imaging, including magnetic resonance (MR) enterography or abdominal MR, abdominal CT, and upper gastrointestinal radiographs with small bowel follow through (UGI-SBFTs) reports were included if they were interpreted by an attending pediatric radiologist at UCSF and were performed within 6 months of the associated procedure date. Microscopic disease extent was determined from review of the pathology report associated with each procedure. Findings considered typical or definitive for colonic Crohn's disease included chronic or chronic active ileitis or colitis, architectural distortion including crypt branching or crypt distortion, non-caseating and non-pericryptic granulomas, fissuring, ulceration or fistula formation, and ileal findings such as acute inflammation and pyloric metaplasia. Histologic findings considered suggestive of upper gastrointestinal (GI) tract involvement included non-caseating granulomas, ulcers, chronic active or chronic inflammation of the esophagus, stomach, and duodenum. As discussed by Turner et al(7), the definition of Crohn's disease in the upper GI tract remains debated. Given this lack of consensus, each reviewer interpreted the findings according to the pathology report and whether the pathologist regarded the findings as consistent with CD or not.

Data were recorded for each encounter and then compiled to create a maximal macroscopic disease location extent diagnosis throughout the patient's lifetime and a second combined diagnosis including microscopic findings. Discordant cases were jointly reviewed to determine the correct classification of disease extent for each patient. This research was approved by the Committee on Human Research at UCSF.

Statistical Analyses

Agreement of disease extent between the reviewers (interobserver agreement) was evaluated using Cohen's kappa statistic (kappa) calculated separately for macroscopic and combined disease extent by anatomic location. A kappa value of 1 indicates perfect agreement between reviewers, while 0 indicates agreement by chance and −1 perfect disagreement. The p-value for the kappa statistic indicates the probability that the obtained value is due to chance(8); therefore, we considered kappa values with a p-value of less than 0.05 correct. Strength of agreement was judged using the categories outlines by Altman (<0.4: Poor or Fair, 0.41–0.6: Moderate, 0.61–0.8: Good, >0.81: Very Good, see Supplemental Digital Content, Table 1). Additionally, we calculated a McNemar's chi^2 to confirm that asymmetry in disagreements was reasonably explained by chance.

Results

Sixty patient records were reviewed independently by the two reviewers to establish (1) the location of disease according to the Paris Classification parameters, and (2) a second combined location classification that included microscopic findings. Macroscopic and combined disease location classification was concordant in 26 (43.3%) patients and discordant in 34 (56.6%). We found no statistically significant differences in demographics or in disease manifestations between patients in whom macroscopic and combined findings were discordant compared with those having concordant findings (Table 1)

Interobserver agreement was analyzed between observers for macroscopic and combined disease classifications independently (Table 2). In ileocolonic disease, the combined classification had a substantially higher kappa value (0.7303, 95% C.I. 0.650–0.821) than the kappa between macroscopic classification (0.5318, 95% C.I. 0.403–0.581). The interobserver agreement regarding classification of upper GI disease proximal to the ligament of Treitz was better in macroscopic compared with the combined classification. Microscopic findings of upper GI tract disease included non-caseating granulomas and chronic active gastritis. Kappa was not calculated for disease distal to the ligament of Treitz, since no microscopic information was available to alter the macroscopic classification (no patients had small bowel biopsies).

Agreement between macroscopic and combined classification was also analyzed both by calculating a kappa coefficient. McNemar's X^2 test was used in order to confirm that asymmetry in disagreements was reasonably explained by chance (Table 3). Table 4 illustrates the differences between distribution of disease location by classification scheme. Agreement between these schemes was moderate (Kappa 0.49, 95% C.I. 0.31–0.68) for ileocolonic disease and poor for upper GI disease proximal to the ligament of Treitz (Paris location L4a) (Table 4). With the combination of macroscopic and histologic findings more patients (n=41, 68.3%) are classified with ileocolonic involvement than using macroscopic data alone (n=26, 43.3%). Under the combined scheme, the percentage of patients with proximal upper GI tract involvement nearly doubles (from 46.7% (n=28) to 85% (n=51), p=0.111).

Discussion

We evaluated interobserver variability of pediatric Crohn disease classification when using two different schemes. Using a randomized cohort of 60 pediatric patients with Crohn's disease followed at UCSF, patients were first assessed according to the Paris Classification (using only macroscopic and imaging findings) and then reclassified with added histologic information. Disease extent classifications differed significantly when comparing isolated macroscopic findings (Paris Classification) with the combined scheme that included microscopy. Inclusion of microscopy decreases variability between observers when assessing disease location in the distal ileum and colon. However, when evaluating upper GI disease involvement, inclusion of microscopy lowers the kappa coefficient, demonstrating increased variability between observers.

Under the combined classification scheme, which included microscopic data, more patients were diagnosed as having extensive ileocolonic disease (L3), in contrast to those with isolated ileocecal (L1) disease or disease limited to the colon (L2). This difference likely explains the improvement in kappa coefficient upon the inclusion of microscopic disease. Inclusion of histologic findings from upper GI involvement lowered interobserver agreement. The variability of upper GI tract findings associated with Crohn's disease, particularly in early and very early onset IBD, and the high prevalence of incidental gastritis in patients with IBD(9–15) could account for this finding. Consequently, the interpretation of histologic findings in the upper GI tract is more challenging than ileocolonic disease,

where inflammation, particularly in the setting of known IBD, is generally considered a sign of active disease.

The Paris classification was created to standardize classification of IBD phenotype in clinical research. Historically, microscopy has not been included in adult classification of IBD(1–3), since in the absence of macroscopic signs of disease histologic findings have not been widely accepted as a sign of active disease. However, it is unclear whether microscopic disease extent can predict characteristics of Crohn's disease such as disease severity and response to medication(16). Inclusion of microscopic findings to characterize Crohn's disease is a relevant discussion, especially as more therapeutic options become available and as goals of treatment broaden to target mucosal disease. Additionally, incorporation of this information decreases the subjectivity and the variability of disease classification. However, by making Crohn's disease phenotype more homogenous with the inclusion of microscopy, more nuanced data about macroscopic disease location may be lost. Furthermore, it remains unclear which scheme provides more accurate representation of disease extent. Ultimately, the goal of disease classification is to better predict outcome by improving phenotype identification.

This study was limited to a single center, which likely introduces little variability in the description and phrasing of findings by endoscopists, radiologists, and pathologists. This may result in systematic bias that may differ from other centers. Additionally, data were collected retrospectively, so determination of macroscopic or microscopic may not have been done independently. The pathologists, endoscopists and radiologists possibly discussed cases and accessed each other's reports, which may have influenced their diagnoses and interpretations of findings. Reviewers collected data solely from these historical reports, a clear limitation, but also concordant with how classification is generally conducted by investigators in the field. Additionally, we did not include disease outcomes or severity of disease over time in our analyses. Thus, from these data we are unable to assess whether disease phenotype is predictive of severity of disease or response to medication over time, a goal beyond the scope of this study but a necessary next step in IBD research since disease classification according to the Paris Classification is utilized increasingly in pediatric IBD research.

Our study demonstrates a difference in extent of pediatric Crohn's disease with inclusion of microscopic disease in contrast to relying on macroscopic disease alone. While the impact of this difference remains unclear, it is important to acknowledge that microscopic findings provide novel information, impact clinical decision making, and may offer a more sensitive view of disease phenotype. Currently, standard practice among pediatric gastroenterologists is to obtain biopsies during endoscopic procedures irrespective of whether macroscopic disease is present, demonstrating that practioners value microscopic information. Thus, serious consideration should be forthcoming to the incorporation of microscopic findings into any IBD classification scheme. More systematic investigation is needed to address the impact microscopic findings have on disease outcomes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. Levine A, Griffiths A, Markowitz J, et al. Pediatric modification of the Montreal classification for inflammatory bowel disease: the Paris classification. Inflamm Bowel Dis. 2010; 17:1314–1321. [PubMed: 21560194]
2. Silverberg MS, Satsangi J, Ahmad T, et al. Toward an integrated clinical, molecular and serological classification of inflammatory bowel disease: report of a Working Party of the 2005 Montreal World Congress of Gastroenterology. Can J Gastroenterol. 2005; 19(Suppl A):5A–36A.
3. Gasche C, Scholmerich J, Brynskov J, et al. A simple classification of Crohn's disease: report of the Working Party for the World Congresses of Gastroenterology, Vienna 1998. Inflamm Bowel Dis. 2000; 6:8–15. [PubMed: 10701144]
4. Russell RK, Drummond HE, Nimmo ER, et al. Analysis of the influence of OCTN1/2 variants within the IBD5 locus on disease susceptibility and growth indices in early onset inflammatory bowel disease. Gut. 2006; 55:1114–1123. [PubMed: 16469794]
5. Vermeire S, Van Assche G, Rutgeerts P. Classification of inflammatory bowel disease: the old and the new. Curr Opin Gastroenterol. 2012; 28:321–326. [PubMed: 22647554]
6. Mazzuoli S, Guglielmi FW, Antonelli E, et al. Definition and evaluation of mucosal healing in clinical practice. Dig Liver Dis. 2013; 45:969–977. [PubMed: 23932331]
7. Turner D, Griffiths AM. Esophageal, gastric, and duodenal manifestations of IBD and the role of upper endoscopy in IBD diagnosis. Curr Gastroenterol Rep. 2009; 11:234–237. [PubMed: 19463224]
8. Viera AJ, Garrett JM. Understanding interobserver agreement: the kappa statistic. Fam Med. 2005; 37:360–363. [PubMed: 15883903]
9. Pascasio JM, Hammond S, Qualman SJ. Recognition of Crohn disease on incidental gastric biopsy in childhood. Pediatr Dev Pathol. 2003; 6:209–214. [PubMed: 12658540]
10. Tobin JM, Sinha B, Ramani P, et al. Upper gastrointestinal mucosal disease in pediatric Crohn disease and ulcerative colitis: a blinded, controlled study. J Pediatr Gastroenterol Nutr. 2001; 32:443–448. [PubMed: 11396811]
11. Abdullah BA, Gupta SK, Croffie JM, et al. The role of esophagogastroduodenoscopy in the initial evaluation of childhood inflammatory bowel disease: a 7-year study. J Pediatr Gastroenterol Nutr. 2002; 35:636–640. [PubMed: 12454578]
12. Valdez R, Appelman HD, Bronner MP, et al. Diffuse duodenitis associated with ulcerative colitis. Am J Surg Pathol. 2000; 24:1407–1413. [PubMed: 11023103]
13. Kundhal PS, Stormon MO, Zachos M, et al. Gastral antral biopsy in the differentiation of pediatric colitides. Am J Gastroenterol. 2003; 98:557–561. [PubMed: 12650787]
14. Parente F, Cucino C, Bollani S, et al. Focal gastric inflammatory infiltrates in inflammatory bowel diseases: prevalence, immunohistochemical characteristics, and diagnostic role. Am J Gastroenterol. 2000; 95:705–711. [PubMed: 10710061]
15. Sharif F, McDermott M, Dillon M, et al. Focally enhanced gastritis in children with Crohn's disease and ulcerative colitis. Am J Gastroenterol. 2002; 97:1415–1420. [PubMed: 12094859]
16. Bryant RV, Winer S, Travis SPL, et al. Systematic review: histological remission in inflammatory bowel disease. Is “complete” remission the new treatment paradigm? An IOIBD initiative. J Crohns Colitis. 2014; 8:1582–1597. [PubMed: 25267173]

What is Known

- Classification of Pediatric Crohn's Disease follows adult schemes by including only macroscopic and imaging findings.
- Biopsies are obtained routinely in endoscopies for Pediatric Crohn's disease, and guide clinical practice.
- There is no evidence that supports or opposes the inclusion of histologic findings in these classifications.

What is New

- There are significant differences in disease location when comparing the current scheme with a new classification including histology.
- The interobserver variability of ileocolonic disease location improves when histology is included.
- Microscopic findings suggestive of Crohn's disease proximal to the ligament of Treitz are more controversial.

Table 1

Concordance between Macroscopic[1] and Combined[2] Classifications for Pediatric Inflammatory Bowel Disease

	Overall	Concordance between Macroscopic and Combined Classifications		p-value[3]
	(n=60)	Yes (n=26)	No (n=34)	
	n(%) or (mean±SD)	n(%) or (mean±SD)	n(%) or (mean±SD)	
Male	37 (61.67)	18 (69)	19 (55.88)	0.29
Age at Diagnosis in Years	10.88±0.56	10.39±0.81	11.25±0.79	0.45
Current Age in Years	16.89±0.52	16.62±0.85	17.11±0.67	0.65
Years since Diagnosis	6.02±0.46	6.23±0.66	5.85±0.65	0.69
Number of endoscopic procedures	1.78±1.46	1.96±1.34	1.65±1.18	0.34
Characteristics per Paris Classification Guidelines[4]:				
Age at Dx category				
A1a (<10 years of age)	24 (40)	12 (46.15)	12 (35.29)	
A1b (10 to <17 years of age)	34 (56.67)	14 (53.85)	20 (58.82)	0.36
A2 (17 to <40 years of age)	2 (3.33)	0	2 (5.88)	
Disease Behavior				
B1 (Non-stricturing, non-penetrating)	50 (83.33)	22 (84.62)	28 (82.35)	
B2 (Stricturing)	8 (13.33)	4 (15.38)	4 (11.76)	0.64
B3 (Penetrating)	1 (1.67)	0	1 (2.94)	
B2B3 (Stricturing & Penetrating)	1 (1.67)	0	1 (2.94)	
Perianal Disease (*p*)	14 (23.33)	6 (23.08)	8 (23.53)	0.97
Growth Impairment (G_1)	8 (13.33)	5 (19.23)	3 (8.82)	0.24

[1] Includes findings from Endoscopy and Imaging.

[2] Combines macroscopic and histologic findings.

[3] Chi2 test for categorical variables, *T-test* for continuous.

[4] As defined by Levine A et al, Pediatric Modification of the Montreal Classification for Inflammatory Bowel Disease: The Paris Classification. Inflamm Bowel Dis 2011: 17 (6). 1314–1321.

Table 2

Interobserver agreement

	Kappa (95% C.I. [Confidence Interval])	
Location	***Macroscopic*[1]**	***Combined*[2]**
L1–3	0.53 (0.40–0.58) *	0.73 (0.65–0.82) *
L4a	0.51 (0.30–0.72) *	0.38 (0.06–0.71) *

[1] Includes findings from Endoscopy and Imaging.

[2] Combines macroscopic and histologic findings

* p-value <0.001

Table 3

Agreement between Macroscopic[1] and Combined[2] Classification

	Kappa (95% C.I.)	p-value	*McNemar's X^2*	p-value
L1–3	0.49 (0.31–0.68)	<0.001	2.88	0.09
L4a	0.14 (−0.03–0.31)	0.0554	2.27	0.13

[1] Includes findings from Endoscopy and Imaging.

[2] Combines macroscopic and histologic findings

Table 4

Disease location according to Macroscopic[1] and Combined[2] Findings.

	Macroscopic Diagnosis	Combined Diagnosis	p-value[3]
Disease Location	**n (%)**	**n (%)**	
Ileocolonic			
None	8 (13.33)	4 (6.67)	<0.001
L1	9 (15)	6 (10)	
L2	17 (28.33)	9 (15)	
L3	26 (43.33)	41 (68.33)	
L4a (Proximal Upper GI tract)	28 (46.67)	51 (85)	0.11

[1] Includes findings from Endoscopy and Imaging.

[2] Combines macroscopic and histologic findings.

[3] Chi2 Test