Journal of the Canadian Association of Gastroenterology, 2020, 3(5), 210–215
doi: 10.1093/jcag/gwz014
Original Article
Advance Access publication 17 May 2019

OXFORD

Original Article

Duodenal Bulb Histology in Paediatric Celiac Disease: A Case–Control Study

Erin Boschee, MD, FRCPC[1], Atilano Lacson, MD, FRCPC[2], Justine Turner, PhD, MBBS, FRACP[3], Jason Yap, MBChB, FRACP[3]

[1]Division of Pediatric Hospital Medicine, Department of Pediatrics, University of Alberta, Edmonton, Alberta, Canada; [2]Department of Laboratory Medicine & Pathology, University of Alberta, Edmonton, Alberta, Canada; [3]Division of Pediatric Gastroenterology, Department of Pediatrics, University of Alberta, Edmonton, Alberta, Canada

Correspondence: Erin Boschee, MD, FRCPC, Department of Pediatrics, University of Alberta, Edmonton Clinic Health Academy, 11405 – 87 Avenue, Edmonton, Alberta, Canada, T6G 1C9, e-mail: boschee@ualberta.ca

Abstract

Background: Controversy exists about optimal methods for duodenal biopsy in diagnosis of celiac disease (CD), in terms of both number of samples and anatomic location. The reliability of duodenal bulb biopsy has been questioned given that normal bulb architecture may mimic disease. However, multiple studies have reported patients with CD have histopathological lesions limited to proximal changes in the duodenal bulb alone.

Methods: We retrospectively compared duodenal and duodenal bulb histology in a population of paediatric patients with CD and compared with a population of nonceliac controls at Stollery Children's Hospital, 2010 to 2012.

Results: Fifty-seven paediatric patients diagnosed with CD and 16 nonceliac controls were included in the study. Fifty-three celiac patients (93.0%) had histopathology consistent with CD (modified Marsh score of 3A, 3B or 3C) in the duodenal bulb. The modified Marsh classification differed significantly between duodenum and duodenal bulb in nine celiac patients (15.8%). Of these, five (8.8%) had Marsh 3 in the bulb and Marsh 0 in the distal duodenum. Among controls, no patients had villous atrophy in either the distal duodenum or duodenal bulb, and all patients had a modified Marsh score of 0 at both sites.

Conclusions: The results of this study reinforce that duodenal bulb samples are critically important for diagnosing CD in paediatric patients. We suggest that duodenal bulb samples be submitted in separate containers from distal duodenal samples to facilitate accurate interpretation. In contrast to prior reports, we found villous blunting and intraepithelial lymphocytosis are actually uncommon findings in paediatric patients with nonceliac gastrointestinal disorders.

Keywords: *Celiac disease; Duodenal bulb; Histology*

Celiac disease (CD) is an autoimmune gluten-dependent enteropathy characterized by mucosal inflammation, villous atrophy and malabsorption in the small intestine of genetically susceptible individuals (1). Immune system activation results in the production of autoantibodies such as anti-tissue transglutaminase (aTTG) and anti-endomysial antibodies (EMA), which are now widely used as a key component of screening and diagnosis of the condition (2). Classical intestinal endoscopic changes include duodenitis, scalloping and blunting of the duodenal folds (3). Histological changes are commonly described according to the modified Marsh-Oberhuber classification, which features three stages of disease severity progressing from intraepithelial lymphocytosis, to crypt hyperplasia, villous blunting and atrophy (4). The preferred diagnostic approach in North America

Received: February 2, 2019; Accepted: April 25, 2019.

involves both serology and confirmatory upper endoscopy with small bowel biopsy.

Controversy exists about the optimal methods for obtaining duodenal biopsy specimens in terms of both number of samples and anatomic location. Duodenal abnormalities in CD can be patchy; so, it is standard practice to collect multiple tissue samples during endoscopy to reduce the likelihood of a false negative diagnosis due to sampling (5–7). Furthermore, the lesions tend to be more significant in the proximal duodenum and so, duodenal bulb biopsies can yield unique histological findings for diagnosis. However, the duodenal bulb has distinctive architecture as a result of increased exposure to gastric acid, with differences reported in villous to crypt ratio compared to the distal duodenum, and the presence of Brunner's glands and lymphoid nodules which may give the appearance of nodularity (8,9). Therefore, historically it has been feared that normal duodenal bulb histopathology may be misinterpreted for pathological villous blunting (10).

Multiple recent paediatric studies have found a small yet significant population of patients with histological changes consistent with CD evident only in the duodenal bulb (11–15). Two recent paediatric studies found lesions limited to the duodenal bulb in approximately 10% of the included patients, drawing the conclusion that routine duodenal bulb biopsy taken during upper endoscopy for CD would increase the diagnostic yield (15,16). European guidelines recommend biopsies from both the duodenal bulb (at least one) and second or third part of the duodenum (at least four). The North American Society for Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN) recommends a minimum of one duodenal bulb biopsy in addition to at least four specimens from the distal duodenum (5,17,18). A recent paediatric study questioned this clinical practice, reporting a high frequency of bulb abnormalities even among control patients (19). Thus, the paediatric literature features disagreement about the prevalence and characteristics of duodenal bulb histopathological abnormalities, and the utility of duodenal bulb biopsy for diagnosis of CD remains uncertain (9,20,21).

We aimed to study the histology of the duodenal bulb as compared to the duodenum in paediatric patients with CD and control patients with nonceliac gastrointestinal disorders. We hypothesized that the presence of abnormalities such as villous atrophy in the bulb would be rare among control patients with nonceliac gastrointestinal disorders but consistent in celiac patients, supporting the reliability of duodenal bulb specimens in CD diagnosis. We also hypothesized that a small but significant proportion of paediatric patients would display histologic discrepancy between the distal duodenum and duodenal bulb, suggesting that duodenal bulb biopsy is important for accurate diagnosis of CD.

METHODS

The research study was approved by the University of Alberta Human Research Ethics Board (Pro00027343). A single author (E.B.) performed chart review and data collection. Celiac patients were identified retrospectively from the Stollery Children's Hospital Celiac Disease Clinic database, 2010 to 2012. During this time period, a routine protocol for all endoscopists to take separate biopsy samples from both the distal duodenum and duodenal bulb had been introduced. The current research overlapped a quality assurance review on the uptake of this newly introduced protocol. The biopsy samples were intended to be collected separately and routinely sent to pathology in separate containers.

Inclusion criteria for celiac patients were: age between 0 and 18 years at the time of biopsy; completed clinical paediatric gastroenterology assessment following referral to rule out CD; completed diagnostic upper endoscopy and duodenal biopsy; collection of biopsy samples from both the duodenum (at least four) and duodenal bulb (at least one), with submission in separate containers; pathology available for review; and subsequent histological diagnosis of CD with modified Marsh Oberhuber duodenal histological classification of grade 3A, 3B or 3C. All consecutive celiac patients meeting the above inclusion criteria were included. Patients following a gluten-free diet at the time of endoscopy and biopsy were excluded, as were those with a previous diagnosis of CD or with nonconfirmatory histology (Marsh grade 0 or 1).

During the same time as cases were identified, control patients were ascertained by one endoscopist (J.Y.) who placed his routinely obtained bulb biopsies in a separate container to distal biopsies in patients undergoing upper endoscopy for suspicion of nonceliac gastrointestinal disorders. These controls were typically patients with functional gastrointestinal disorders (Table 2). All consecutive patients meeting inclusion criteria were included. Criteria for inclusion for control patients were: age between 0 and 18 years at the time of biopsy; completed clinical paediatric gastroenterology assessment following referral for gastrointestinal complaints, excluding suspicion of CD; completed diagnostic upper endoscopy and duodenal biopsy; separate collection of biopsy samples from both the duodenum and duodenal bulb with a minimum of one sample collected from the bulb, and bulb and duodenal specimens submitted in separate containers; pathology available for review and no histological diagnosis of CD. Control patients following a gluten-free diet at the time of endoscopy and biopsy were excluded.

Case and control patients meeting inclusion criteria were identified, and patient charts were reviewed for demographic information, presenting symptoms (if any) and biopsy results per the original histopathology reports. Demographic information collected included age at the time of biopsy, gender and growth parameters. Serological test results, including serum aTTG,

immunoglobulin A (IgA) and EMA, were recorded. Missing demographic, symptom or laboratory data were assumed to be negative (in the case of categorical variables like presenting symptoms) or zero (in the case of continuous variables such as serological results), to underestimate, as opposed to overestimate, results. Upper endoscopy had been performed by one of five local paediatric gastroenterologists, and biopsy specimens were interpreted by one of two paediatric pathologists who were not blinded to the patients' clinical data, including demographic information, presenting symptoms and laboratory results. The pathologists used the modified Marsh Oberhuber classification to interpret duodenal bulb and distal duodenal samples. IELs were not counted specifically but were reported as greater or less than 30.

Quality of interpretation of the original histopathology reports was confirmed via blinded review by a single paediatric pathologist (A.L.), who reviewed all available duodenal bulb and distal duodenal specimens of control patients and an equal number of celiac patients who were individually age and gender-matched to controls. Blinding of the specimen slides was done by a single author (E.B.). The pathologist was blinded to all patient information, including study classification as a case or a control, demographic information, presenting symptoms, serological results, endoscopic findings and original histopathological interpretation. Criteria for Marsh 3, with a minimum number of IELs of 30, were applied for the blinded review.

Statistical analysis was performed using SPSS software (version 25). Continuous variables were expressed as means with standard deviations. Comparisons utilized Student's *t* test for continuous data or Pearson chi-square analysis for frequencies. Significance was defined by *P*-value of less than 0.05. Sensitivity and specificity were calculated to represent the diagnostic accuracy of duodenal bulb biopsy, and reported with 95% confidence intervals.

RESULTS

Of 140 paediatric patients who underwent upper endoscopy and were diagnosed with CD from 2010 to 2012 at our institution, 58 had duodenal bulb and distal duodenal biopsy specimens submitted in separate containers. Fifty-seven celiac patients met inclusion criteria (Figure 1), having a modified Marsh score of 3 in at least one of the distal duodenum or duodenal bulb, and at least one bulb and four distal duodenal biopsy specimens submitted separately from each anatomical site. One of the 58 identified celiac cases was excluded as they had a modified Marsh score of 2 in both the distal duodenum and duodenal bulb; this patient received a clinical diagnosis of CD in the context of these biopsy findings, classical gastrointestinal symptoms and a significantly elevated aTTG (3550IU). Seventeen potential control patients were identified. Sixteen of these patients met inclusion criteria; one was excluded as they were on a gluten-free diet at the time of biopsy.

Demographics were similar between groups (Table 1). The mean age at the time of biopsy among celiac patients was 9.7 years (±4.3 years) and among control patients it was 11.2 years (± 4.2 years). Thirty celiac patients were male (52.6%) and nine control patients were male (56.2%). The most common presenting symptom among both groups was abdominal pain (59.6% among celiac patients and 87.5% among controls) (Table 1). Additional common presenting symptoms among celiac patients were bloating, constipation, diarrhea and fatigue. Other common presenting symptoms among control patients included diarrhea, vomiting, constipation, fatigue and headache. The mean aTTG was 354.1 U/mL for celiac patients compared with 1.3 U/mL among controls. The most common diagnoses among control patients were functional gastrointestinal disorders, including functional dyspepsia, irritable bowel syndrome and functional constipation (Table 2).

Among CD patients, the average number of distal duodenal specimens was 5.9 (range 4 to 9) and of bulb specimens was 1.9 (range 1 to 3); both were always submitted separately. Villous blunting was present in 52 celiac patients (91.2%) in the distal duodenum, and in 54 celiac patients in the duodenal bulb (94.7%). Fifty-two (91.2%) of celiac patients were modified Marsh 3A, 3B or 3C in the distal duodenum and 53 cases (93.0%) had pathology consistent with modified Marsh 3A, 3B or 3C in the duodenal bulb (Table 3). Three patients (5.4%) were found to have typical celiac pathological changes present only in the distal duodenum, two of which were Marsh 3A in the duodenum and Marsh 0 in the bulb, and one who was Marsh 3B in the duodenum and Marsh 0 in the bulb. The modified Marsh classification was 0 among 5 CD patients in the distal duodenum (8.8%), with those patients having biopsies consistent with CD present only in the duodenal bulb (three patients were Marsh 3A in the bulb and two patients were Marsh 3B). Histopathology was consistent between duodenal bulb and distal duodenum (same numerical Marsh grade) in 48 (84.2%) celiac cases. The sensitivity and specificity of duodenal bulb biopsies for CD diagnosis in confirmed celiac cases were 92.3% (95% confidence interval [CI]: 83.0 to 97.1%) and 100% (95% CI: 79.4 to 100.0%), respectively.

Among control patients, the average number of distal duodenal specimens was 4.1 (range 2 to 6) and the average number of bulb specimens was 2.0 (range 1 to 3); distal duodenal and bulb specimens were submitted separately. Distal duodenal histology among control patients revealed no intraepithelial lymphocytosis, lamina propria inflammation, crypt hyperplasia or villous atrophy and all 16 patients had a modified Marsh score of 0 (Table 3). No control patient had crypt hyperplasia or villous atrophy in the duodenal bulb, and all 16 patients were duodenal bulb modified Marsh 0 (Table 2).

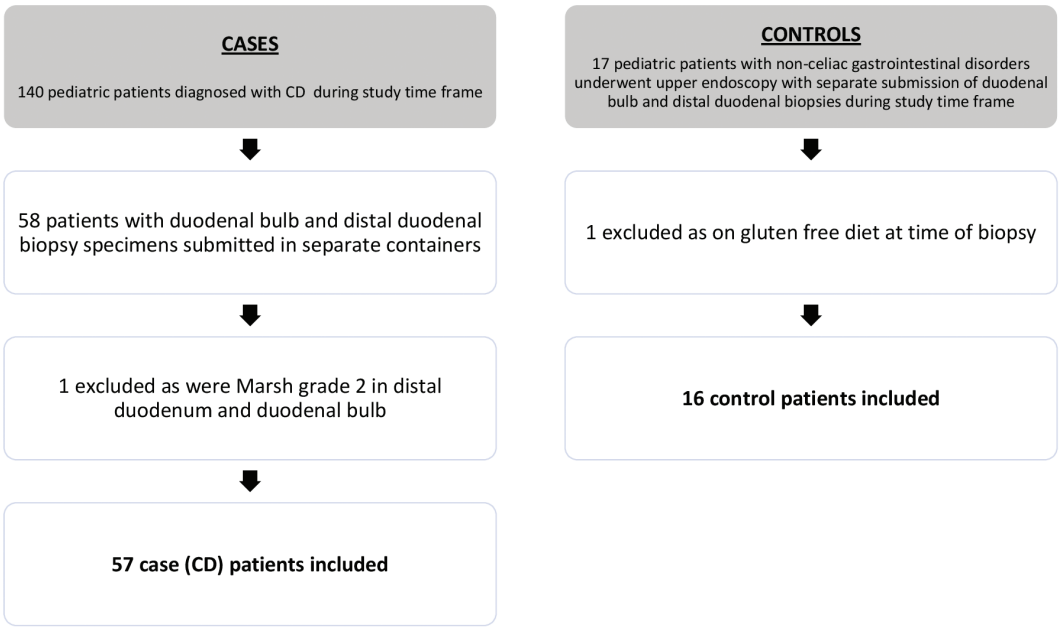

Figure 1. Flow diagram of study participants at Stollery Children's Hospital between 2010 and 2012.

Table 1. Demographic and clinical features of paediatric celiac patients and paediatric controls with nonceliac gastrointestinal disorders

Demographic and clinical variables	Case (n = 57) (mean [SD])	Control (n = 16) (mean [SD])	P value
Age (years)	9.7 (4.3)	11.2 (4.2)	0.24
Gender (M:F) (*n*)	30:27	9:7	0.80
Weight (kg)	35.8 (18.7)	41.2 (16.7)	0.36
Height (cm)	138.2 (26.3)	139.8 (21.2)	0.85
BMI (kg/m^2)	18.0 (4.6)	20.0 (3.6)	0.16
aTTG (IU)	354.1 (499.8)	1.3 (0.9)	0.023
Biopsies distal (*n*)	5.9 (1.1)	4.1 (1.2)	<0.001
Biopsies bulb (*n*)	1.9 (0.5)	2.0 (0.4)	0.57
Common Presenting Symptoms*			
Abdominal pain (*n*)	34 (59.6%)	14 (87.5%)	0.034
Bloating (*n*)	18 (31.6%)	1 (6.3%)	0.06
Diarrhea (*n*)	15 (26.3%)	5 (31.3%)	0.49
Vomiting (*n*)	4 (7.0%)	5 (31.3%)	0.003
Constipation (*n*)	17 (29.8%)	3 (18.8%)	0.68
Poor weight gain or weight loss (*n*)	16 (28.1%)	3 (18.8%)	0.36
Asymptomatic (*n*)	8 (14.0%)	1 (6.3%)	0.28

*The number of patients where presenting symptoms were recorded varied; hence, the frequency of symptoms presented above may differ from the true frequencies among the case and control groups.

History (presence or absence) of presenting symptoms was recorded/available for: abdominal pain (91.2% of cases, 93.8% of controls); bloating (80.7% of cases, 62.5% of controls); diarrhea (84.2% of cases, 81.3% of controls); vomiting (80.7% of cases, 75% of controls); constipation (80.7% of cases, 75% of controls); poor weight gain or weight loss (87.7% of cases, 62.5% of controls); asymptomatic (98.2% of cases, 100% of controls).

Discussion

The results of this study suggest that duodenal bulb pathology is representative of distal duodenal pathology in a majority of cases of paediatric CD and is an important component of biopsy diagnosis. Ninety-three per cent of celiac patients in our study had a modified Marsh score of 3(A-C) in the duodenal bulb. Histopathology was consistent between sites (same numerical Marsh grade) in 84.2% of cases. Additionally, five

patients (8.8%) had normal pathology in the distal duodenum, but had a modified Marsh score of 3 in the duodenal bulb, suggesting that these cases would have been missed had separate bulb specimens not been submitted at the time of upper endoscopy. No control patient in our study had villous blunting or intraepithelial lymphocytosis reported in the duodenal bulb, suggesting that the presence of such abnormal findings in the duodenal bulb is reliable for CD.

At the time that this study was conducted, the uptake among endoscopists at our institution of separating duodenal bulb biopsies in suspected celiac cases was poor (only 41%). As a quality assurance endeavour, this study reinforced the need for better adherence to guidelines that recommend submission of both distal duodenal and duodenal bulb biopsies in separate containers, as had been introduced at our own institution. The study allayed fears that false-positive diagnosis of CD could result from the misinterpretation of normal bulb histology, given that no features consistent with CD pathology were observed in the control patients. While it has been suggested that typical architecture of the duodenal bulb may be misinterpreted for pathological villous blunting, the findings in this study support the reliability of pathological changes in the duodenal bulb representing CD.

Table 2. Gastrointestinal diagnoses of nonceliac controls made by paediatric gastroenterologist based on presenting symptoms, laboratory investigations, upper endoscopy and histological results

Diagnosis	Number of patients (n = 16)
Functional dyspepsia	5 (31.3%)
Irritable bowel syndrome	2 (12.5%)
Esophagitis	2 (12.5%)
Functional constipation	1 (6.3%)
Functional diarrhea	1 (6.3%)
Post-infectious irritable bowel syndrome	1 (6.3%)
Abdominal migraines	1 (6.3%)
Family history of familial adenomatous polyposis	1 (6.3%)
Not available	2 (12.5%)

Mucosal changes in CD are known to be patchy in children. Given the potential for patchy disease, current North American guidelines for diagnosis of CD in children recommend at least four histologic samples from the distal duodenum and one or two from the duodenal bulb (17). The optimal number of samples required for diagnosis remains uncertain. Weir et al. studied 101 children with CD with biopsies taken from the duodenal bulb and second portion of duodenum and reported variation in pathology, whereby normal mucosa and CD changes were found concurrently in a single biopsy fragment in 18% of the cases (11). The prevalence of patchiness, which they defined as variation of at least one Marsh grade between separate fragments in a biopsy set, in their study population was 53% (11). In contrast, Prasad et al. studied duodenal bulb histology in 52 consecutive children with CD and found that 86.5% of CD patients had lesions of identical type (2 or 3) in the distal duodenum and duodenal bulb (9). Mangianvillano et al. found that histology was the same in the bulb and duodenum in 35 out of 47 celiac patients (74.5%) (12). Our findings revealed consistency (same numerical Marsh grade) between duodenal sites in 48 patients (84.2%).

The frequency of histopathological changes limited to the duodenal bulb was 8.8% in celiac patients in our study, which is comparable to current literature. Rashid and MacDonald reported that 4 of 35 paediatric celiac patients studied (11.4%) had disease limited to the duodenal bulb (15). Levinson-Castiel et al. found 7% of the patients with typical histologic findings only present in the bulb (22). Weir et al. found a rate of isolated CD bulb findings in 9.9% (11) of cases and Mangiavillano et al. found a rate of 10.6% (12). The relatively small but clinically significant number of patients with pathological changes isolated to the duodenal bulb in the literature and this study supports the essential nature of bulb specimens as part of CD diagnosis.

This study has a few limitations. As it was a retrospective review, multiple practitioners were involved in performing endoscopy for cases (5), and as routine separation of biopsies from bulb and distal duodenum was not routine for controls,

Table 3. Histopathology results among paediatric celiac patients and control patients in the distal duodenum and duodenal bulb

Modified Marsh classification	Cases		Controls	
	Duodenal bulb	Distal duodenum	Duodenal bulb	Distal duodenum
0	3 (5.3%)	5 (8.8%)	16 (100%)	16 (100%)
1	0	0	0	0
2	1 (1.8%)	0	0	0
3A	19 (33.3%)	21 (36.8%)	0	0
3B	17 (29.8%)	16 (28.1%)	0	0
3C	17 (29.9%)	15 (26.3%)	0	0

controls were only available from one endoscopist. Two paediatric pathologists were involved in interpreting histological specimens; so, variations in interpretation and diagnosis between individuals may have occurred. Neither of the pathologists were blinded to the patients' clinical history, which could also have influenced their interpretation of histologic findings.

CONCLUSION

The results of this study reinforce that duodenal bulb samples are critically important for diagnosing CD in paediatric patients. We suggest that bulb samples be submitted in separate containers from distal duodenal samples to facilitate accurate interpretation. Histopathology was consistent between duodenal bulb and distal duodenum (Marsh type 3) in 84.2% of celiac cases. Duodenal bulb pathology consistent with CD was present in 93.0% of the celiac patients in our study, and 8.8% of the celiac patients displayed pathology confined to the duodenal bulb. In contrast to prior reports, we found villous blunting and intraepithelial lymphocytosis are actually uncommon findings in paediatric patients with nonceliac gastrointestinal disorders.

ACKNOWLEDGEMENTS

This research has been funded by the generous support of the Stollery Children's Hospital Foundation through the Women and Children's Health Research Institute.

Conflicts of Interest

The authors have no conflicts of interest to declare.

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