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ORIGINAL ARTICLE

A prospective study to evaluate the role of duodenal bulb biopsy in the diagnosis of celiac disease

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Abstract

Background Celiac disease (CeD) requires a biopsy from the small intestine to confirm the diagnosis. Conventionally, duodenal bulb (D1) was avoided as a biopsy site due to histological confounding factors at this site. However, sometimes, the bulb mucosa is the only affected site. The aim of the present study was to assess changes in duodenal bulb histology and compare it to distal duodenal histology and to analyze whether the addition of duodenal bulb biopsy increases the diagnostic yield of the CeD.

Methods It was a prospective study comprising of 98 patients of CeD who were symptomatic clinically and had positive anti tissue transglutaminase (tTG) antibody. Endoscopically four mucosal biopsies were taken, two each from the bulb and distal duodenum, and morphology was graded as per modified Marsh grade.

Results Iron deficiency anemia (40%) was a most common clinical presentation followed by chronic diarrhea (30%). Sixty patients showed same Marsh grade and 38 showed different Marsh grade at both sites. Patients who were showing the difference in the Marsh grade at the two biopsy sites, in place of; descending duodenum showed higher grade in 24 patients while higher mucosal atrophy was documented in the bulb in 14 patients. No patient of CeD had isolated D1 involvement. In eight patients, the correct diagnosis of CeD could be made only because of bulb biopsy.

Conclusion Majority of the patients had no classical symptoms. Different Marsh grade at the two biopsy sites was documented demonstrating the patchy distribution of CeD. Combining biopsy from both bulb and descending duodenum maximizes the diagnostic yield of the CeD.

Keywords Celiac disease · Duodenal bulb biopsy · Marsh grade

Introduction

Celiac disease (CeD) is an immune-mediated gastrointestinal (GI) disorder triggered by dietary gluten in genetically susceptible persons. Gluten is a composite group of proteins found in wheat, rye, and barley. CeD is characterized by wide-ranging clinical presentations, a specific serum antibody response and histological demonstrable damage to small intestinal mucosa [1]. Internationally, the prevalence of CeD is known to be 0.2% to 1.0% [2–4], while in India, the prevalence of CeD in children varies from 0.3% to 1% [5, 6]. Prevalence of CeD in adults is highly variable in different regions of India; it was reported as 8.53/1000 in northern, 4.66/1000 in north eastern, and 0.11/1000 in the southern part of India [7]. This difference is due to different dietary habits across India. Despite increased awareness, CeD patients represent only tip of the iceberg. A recent study from the UK reported that only 25% patients with CeD currently are diagnosed [8].

In the pre-endoscopic era, small bowel biopsies were taken from the jejunum with a Crosby capsule to diagnose CeD [9]. However, with the advent of fiberoptic endoscopy, biopsies from the distal duodenum were shown to be as sensitive as jejunal biopsy specimens for documenting the mucosal changes in CeD [9]. The gluten load is highest in the proximal GI tract and the duodenal bulb (D1) would seem to be the ideal place to identify maximum mucosal changes of the CeD. Additionally, a proximal to distal gradient could also exist in the enteropathy, as gluten reaches the bulb first [10]. However, histologically D1 is a site which harbors Brunner's glands resulting in a reduced villous height and therefore was avoided

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as a possible biopsy site because of concerns over the difficulty in interpretation. In addition, peptic duodenitis and the potential presence of gastric metaplasia at D1 make a histological diagnosis of CeD difficult [11, 12]. However, recently, a study has suggested that interpretation of D1 biopsies is possible and that it may be the only site of villous atrophy in newly diagnosed CeD [10, 12]. But this increased rate of detection by adding a D1 biopsy has not been proven in other studies [13].

Hence, we wanted to verify this concept that whether the addition of duodenal bulb biopsies to distal duodenum biopsies would increase the diagnostic yield of CeD and whether there was any difference in the histological grading between the two biopsy sites.

Aim and objective

1) To assess the utility of duodenal bulb biopsy in patients of clinically suspected CeD having positive celiac serology
2) To compare the histological findings (modified Marsh grading) of duodenal bulb and descending duodenum biopsies

Method

Patients and sampling

It was a prospective study conducted from June 2015 to May 2017 at Department of Gastroenterology, SMS Medical College, Jaipur. Patients presenting with signs and symptoms such as chronic diarrhea with or without features of malabsorption, refractory iron deficiency anemia, poor growth, or short stature for age, etc. and having positive celiac serology (IgA anti-tTG > 15 AU/mL, measured by enzyme immunoassay) along with written consent were included. Patients who were already diagnosed with a CeD were excluded from the study. A total of 98 patients could satisfy the inclusion criteria during the study period and were evaluated according to the study protocol. This study was approved by ethics committee of the institution. The patients underwent endoscopy (Olympus 150 series) and duodenal biopsies were obtained (two from duodenal bulb and two from descending duodenum). Each biopsy was mounted on a filter paper and oriented so that the luminal surface was uppermost and fixed in 10% neutral formalin. Patients were defined as having CeD if they had a combination of positive IgA tTG along with histological evidence of increased intraepithelial lymphocytes (IELs), crypt hyperplasia, and villous atrophy (modified Marsh 3a–3c) in any of their biopsies [14].

Microscopic assessment

Biopsies were stained with hematoxylin and eosin (H&E) and were assessed by a single experienced pathologist. All histologic parameters were evaluated and classified according to the Oberhuber modification of Marsh classification [15]: type 0 = normal mucosa; type 1 = infiltrative (with 40 intraepithelial lymphocytes/100 epithelial cells); type 2 = crypt hyperplasia; type 3a = mild villous atrophy; type 3b = marked villous flattening; and type 3c = total villous atrophy.

Results

Demographics and clinical presentation of CeD

The mean age of the 98 patients evaluated in the study at diagnosis was 35.4 years (range 2–60 years). The median duration of symptoms before diagnosis was 4.2 years (range 6 months to 42 years). Out of 98 patients, 44 were male and 54 were female (M:F 0.81:1).

Iron deficiency anemia (40%) was the most common presentation followed by chronic diarrhea (30%). Rest other had varied presentations in the form of short stature, chronic pain abdomen, cirrhosis, and infertility (Table 1).

All the patients had raised IgA tTG level which ranged from 20 to 250 AU/mL, mean 116.9 ± 51.8 AU/mL.

Histopathology features

Most of our patient's biopsies showed modified Marsh type 3 histology (IELs > 30/100 enterocytes, villous atrophy either partial/subtotal/total, altered villous/crypt ratio, and crypt hyperplasia) of which type 3c was the most common (44.8%). All celiac disease patients had evidence of villous atrophy in at least one biopsy site (bulb or descending duodenum). The classic total villous atrophy (type 3c lesion) in at least one biopsy site was found in 40/98 (40.8%) bulb and 48/98 (48.9%) descending duodenum. Type 1 morphology was uncommon finding which showed only raised IELs. In our study, only 13 patients showed type 2 morphology (Table 2).

Table 1 Presenting symptoms of celiac disease

Presenting symptom	Number	Percentage (%)
Refractory iron deficiency anemia	39	40
Chronic diarrhea	29	30
Short stature	12	12.20
Chronic pain abdomen	8	8.16
Cirrhosis	7	7.14
Infertility	3	3.06
Delayed puberty	1	1.02

Table 2 Histological grading of biopsies from duodenal bulb and descending duodenum according to modified Marsh criterion

Histology grading (modified Marsh)	1	2	3A	3B	3C
D1(duodenal bulb)	3 (3%)	5 (5.1%)	12 (12.2%)	38 (38.7%)	40 (40.8%)
Descending duodenum	0 (0%)	8 (8.1%)	8 (8.1%)	34 (34.6%)	48 (48.9%)
Total	3 (1.5%)	13 (6.6%)	20 (10.2%)	72 (36.7%)	88 (44.8%)

Out of 98 patients, 60 showed homogenous histological appearance with same Marsh grade in both bulb and descending duodenum. While in 38 patients, histological appearance was heterogeneous with 24 patients showing higher grades in descending duodenum and 14 patients showing higher grades in bulb biopsies. But no CeD patient had histologically normal biopsies at any one site.

In all patients with CeD, the duodenal IELs were increased (> 30 IELs/100 enterocytes) at both the sites. The mean IEL in the bulb biopsy was 82 ± 2.9 (range, 36 to 129) while in the descending duodenum biopsy was 85.0 ± 3.2 (range, 39 to 138). In 32 patients, a number of IELs/100 enterocytes were different in bulb and descending duodenum. Of them, 20 patients showed higher IEL/100 enterocyte count in descending duodenum while the remaining 12 had a higher count in duodenal bulb (Fig. 1).

Discussion

In India, the CeD was first reported in 1966 in children by Walia et al. [16] and in adults by Misra et al. [17]. These days, CeD is being recognized more frequently possibly reflecting increasing awareness resulting in a higher index of clinical suspicion and availability of improved diagnostic tests. Currently, the mean age of presentation is 45 years [18]. In our study including both pediatric and adult patients, mean age of presentation was 35.4 years (range 2 to 60 years).

Celiac disease is now being diagnosed increasingly even in those patients who present with non-classical symptoms. Earlier studies from India reported diarrhea as the most common presenting symptoms [19–21]. However, recent reports from both pediatric and adult age groups have shown that majority of the patients have non-classical celiac diseases (NCCeD) [22, 23]. In our study, also, most of the patients had NCCeD type presentation. Iron deficiency anemia (40%) was the most common presenting symptom followed by chronic diarrhea (30%), short stature (12.2%), chronic pain abdomen (8.1%), and infertility (3%).

The ACG guidelines 2013 require medical history, physical examination, serology, and upper endoscopy with histological analysis of multiple biopsies of the duodenum for the confirmation of a diagnosis of CeD [24]. The proximal jejunum and distal duodenum are commonly considered the optimal sites for the detection of subtotal/total villous atrophy in CeD [25, 26]. However, higher grade of histological changes in bulb compared to

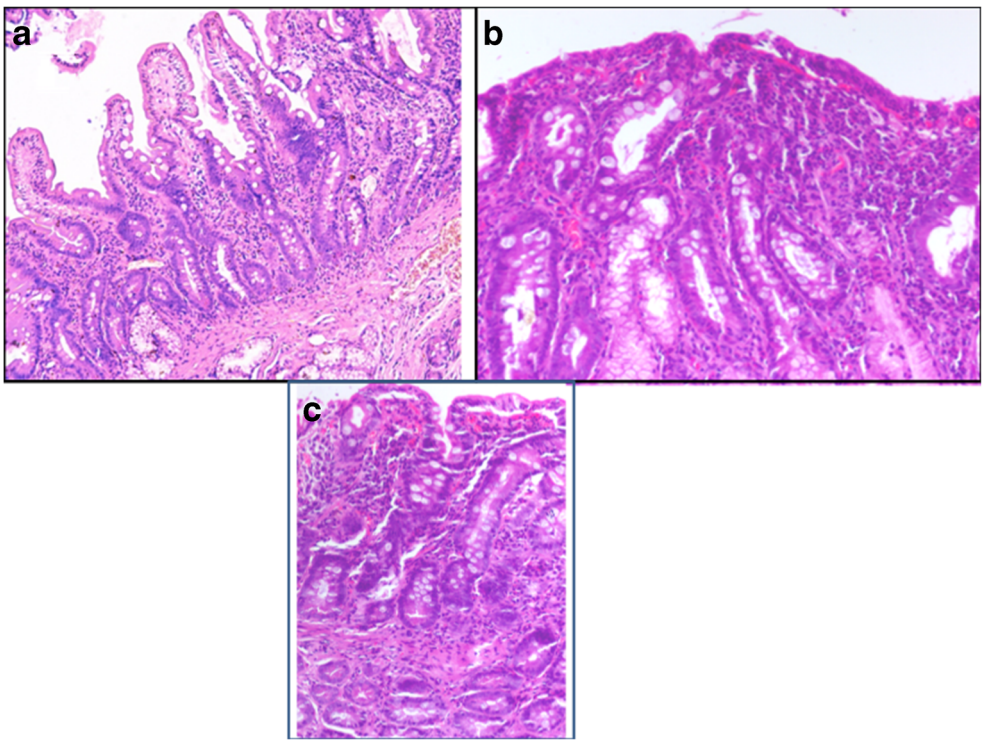

Fig. 1 Panel of microphotographs depicting morphological changes in duodenal biopsies. **a** Micrograph shows normal duodenal bulb mucosa (D1) with Bruner's glands (black arrow) (H&E sectioned, 40×). **b** Micrograph from duodenal bulb (D1) shows partial villous atrophy, crypt hyperplasia, and raised IELs (H&E sectioned 40×). **c** Micrograph from distal duodenum shows partial villous atrophy, crypt hyperplasia, and raised IELs (H&E sectioned 40×)

descending duodenum has been reported [27, 28]. In fact, there have been reports that few cases may not show histological signs of the CeD on biopsy from the descending duodenum, even in the presence of CeD compatible histology at duodenal bulb [27]. In the present study, 14 patients had a higher histological grade in bulb than descending duodenum and of them, in eight patients, distal duodenum did not have evidence of villous atrophy. In these eight patients, correct diagnosis of CeD would not have been possible without bulb biopsy. Thus, in our study, duodenal bulb biopsy resulted in an increase in diagnostic yield.

Recently, there have been a few reports identifying isolated D1 involvement with normal appearing mucosa in the distal duodenum in CeD patients in pediatric and adult age groups [11, 29]. But in our study, no patient of CeD had isolated D1 involvement with completely normal histology at descending duodenum. The possible reason for the discrepancy in this finding could be that all our patients were newly diagnosed CeD and we did not study known CeD patients who had long been on a gluten-free diet and had recently started a gluten challenge as proposed by Vogelsang et al. [12].

There were a few limitations in the present study. IgA tTG was the only serological test used in our study, so patients with IgA deficiency might have been inadvertently excluded. This was a hospital-based study so it might not be the representative of the whole population. The conclusion of the study might be limited by the small sample size of the study.

The clinical picture of CeD has changed over the years. Many patients present with non-diarrheal disease, and hence, a high index of suspicion is necessary. Biopsies from both duodenal bulb (D1) and descending duodenum are mutually exclusive. In our study, bulb and descending duodenal biopsies individually were diagnostic in nearly 92% of the patients, so they were equally representative. However, different Marsh grades can be seen in the same patient at the two biopsy sites which confirms the patchy nature of the disease. The diagnostic yield can be increased by combining biopsies from both sites.

Compliance with ethical standards

Conflict of interest BSD, GKG, SJW, NS, and SN declare that they have no conflict of interest.

Ethics statement The authors declare that the study was performed in a manner conforming to the Helsinki declaration of 1975, as revised in 2000 and 2008 concerning human and animal rights, and the authors followed the policy concerning informed consent as shown on Springer.com.

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