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Value of Duodenal Bulb Biopsy in the Diagnosis of Celiac Disease in a Group of Iranian Children

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Abstract

Background: Studies have shown that Celiac Disease (CD) can present with patchy mucosal lesions. The aim of this study is to investigate the utility of duodenal bulb biopsy in the diagnosis of CD in some Iranian children. Moreover, we compare disease characteristics in children with CD consistent histology limited to the duodenal bulb (D1) with those of children with CD-related histology in the second part of duodenum (D2) with or without histology changes in D1.

Methods: This is a cross sectional study on anti-tissue transglutaminase antibody (anti TTG Ab) positive children in Mashhad between 2019 and 2021. Intestinal biopsies from D1 and D2 were done. Diagnosis of CD was defined by the Marsh classification above 1. Patients of 2 groups compared in terms of clinical and laboratory parameters.

Results: from 81 serology positive patients, 70 patients were diagnosed with CD, based on Marsh classification. Among them, 6 patients (8.6%) had exclusive involvement of D1, and 64 cases (91%) had involvement of D2 with or without D1. The two groups did not have a statistically significant difference in terms of clinical presentation, serological and histopathological values.

Conclusion: Taking D1 biopsies can improve case finding of CD in the pediatric population.

Key Words: Abdominal pain, Celiac disease; Child, Short stature, Tissue transglutaminase 2.

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1- INTRODUCTION

Celiac Disease (CD) is an immune-mediated enteropathy caused by a permanent sensitivity to gluten and other related proteins in barley and rye in genetically susceptible children and adolescents (1, 2). The prevalence rate of CD is 1 % among the general population of Europe and North America (3-5). As a result of untreated CD, the patients may experience various complications and long-term increases in mortality and morbidity (6, 7). Therefore, the importance of an early and accurate diagnosis of CD cannot be over-emphasized (8, 9). The diagnostic elements of CD generally include clinical presentation, positive CD—specific serology, and characteristic histological findings in small bowel biopsies (6-10). Clinical scenarios of CD are changing and variable over years and the diagnosis are shifted to be based on highly specific and sensitive CD related serological tests and duodenal pathology (11). According to ESPGHAN guidelines for CD management, small bowel biopsy remains the gold standard for diagnosis in both pediatric and adult populations (12). Historically, the second part of duodenum (D2) was proposed as the main site for the biopsies taken during the endoscopy (13-15). Several studies that were inspired by the concept of the patchy nature of CD demonstrated that adding biopsies of the first part of the duodenum (D1) can reduce the missed diagnosis of CD cases (16-18). Indeed, several clinicians reported individuals with CD-compatible histological changes limited to the D1 with no histological changes in D2 in both adults and children, which increases the diagnostic yield of CD (19-21). Some studies have established that patients with isolated D1 mucosal abnormalities characteristic of CD (ultra-short celiac disease, USCD) had milder clinical symptoms, and lower titers of anti-tissue transglutaminase antibodies (Anti TTG IgA) at diagnosis (20-22). Nevertheless, one study showed no difference in clinical and pathological values in children with USCD and children with CD involving the second part of the duodenum (extensive CD) (23). Comparison of the clinical features of children with USCD and extensive CD has not yet been investigated. The purpose of this study was to investigate whether adding D1 biopsies improves the power of this diagnostic tool in better case finding of CD. In the further analysis, we set out to investigate the comparison of demographic, clinical, pathological, and serological characteristics at baseline between children with USCD and children with extensive CD.

2- MATERIALS AND METHODS

All children below 18 years of age with 2 positive Anti-TTG IgA who referred to Akbar's children hospital, Mashhad, Iran, were included in the study and underwent esophagogastroduodenoscopy (EGD) between 2019 and 2021. For all patients, two biopsies were taken from D1 and four biopsies from D2. Biopsies were instantly fixed in 10% formalin, processed and colored with Haematoxylin and Eosin (H&E) and reported by expert pathologists in conformity with the modified Marsh-Oberhuber classification. This classification has 4 scores: 0: normal intestinal mucosa, 1: infiltration of more than 25 intra-epithelial lymphocytes (IELs) per 100 enterocytes (infiltrative lesion), 2: increased IELs and crypt hyperplasia (hyperplastic lesion), 3: increased IELs, crypt hyperplasia and villous atrophy (destructive lesion) with three subgroups of 3a (mild villous atrophy), 3b (moderate villous atrophy), 3c (severe villous atrophy). CD was ruled out for subjects with Marsh grade 0 or 1 in biopsy results in both sites and these patients were excluded from the study. Subjects with Marsh scores above 1 were considered as

CD patients and divided into 2 groups. Patients with Marsh scores above 1 in D1 alone (USCDs) and D2 with or without D1 (extensive CD) were placed in groups one and two, respectively. Demographic and anthropometric parameters, clinical manifestations, family history of CD, and laboratory data were collected at diagnosis. We also recorded the endoscopic gross appearance of the gastric and duodenal mucosa along with histopathological findings. The two groups were compared clinically and laboratory. Descriptive statistics were performed for all variables including mean and standard deviation (mean± SD) for normally distributed data. Quantitative variables were analyzed by the T student test, Mann- Whitney, ANOVA and Tukey's test. P-value less than 5% was considered as statistically significant.

3- RESULTS

3-1. Baseline Characteristics

A total of 81 children with two positive anti-TTG IgA tests enrolled in this study. The age range of cases was 9 months to 13.5 years with the mean age of 5.4 years. All cases underwent EGD and intestinal biopsy taken from D1 and D2. From these 81 patients, eleven patients had a modified Marsh score of 0 or 1 in both sites which were excluded from the study. 6 cases (8.6%) had Marsh score 2 or 3 in D1 (group 1, USCD) and 64 (91%) cases had D2 involvement with or without pathological findings in D1 (group 2, extensive CD). Demographic data, clinical presentation, serological values, and histopathological findings were compared between the two groups (**Table 1**). Female predominance was observed in both groups. Children with extensive CD had lower mean body mass index (BMI) than children with USCD, although the difference was not significant (14 vs 15.7, P-value: 0.06). Moreover, there were no noticeable differences in demographic details and family history of CD among the children with USCD compared to extensive CD patients.

3-2. Symptoms and Celiac Serology

Among all cases, the most clinical presentations were poor weight gain (42.8%), chronic abdominal pain (39, 5%), bone pain (37.1%), and chronic diarrhea (25.7 %), respectively. Abdominal pain was the main clinical feature in extensive CD children, whereas short stature was the main manifestation among children with USCD (**Table 1**). The mean Anti- TTG-IgA level at diagnosis was 184±174 IU/ml. The mean Anti TTG-IgA level in extensive CD cases was more than 2-fold of USCDs (195±178 vs 75±61), but the difference was not statistically significant (P= 0.11). We also found that from 40 subjects who had Anti-TTG IgA levels more than 10 times of the normal level (120 U/ml); 35 of them had Marsh grade 3 in at least one site. 22 patients had Anti TTG-IgA level>300 U/ml, and all of them showed Marsh Grade 3 morphology in at least one site. None of the children in USCD group had Anti TTG-IgA more than 300 U/ml. None of cases had IgA deficiency.

3-3. Gross endoscopic findings

Normal gross upper endoscopy appearance was more evident in D1 than in D2 (42% vs. 15%) (**Table 1**). The most abnormal pattern in gross appearance was cobblestone appearance that was shown in 15 and 35 cases in D1 and D2, respectively. Among 30 individuals with normal endoscopic gross appearance in D1, 22 patients had Marsh score 2 and 3. Among 10 cases with normal endoscopic appearance at D2, 7 had Marsh score 2 and 3 (**Table 1**).

3-4. Histopathology findings in D1 and D2

Biopsy results showed CD-compatible histology (Marsh score 2, 3) in 59 cases (84%) in D1 and 64 (91.4%) in D2 (**Table 2**).

Table-1: Demographic data, clinical presentations, serological values, endoscopic and histopathological findings

Parameter	total	Children with USCD	Children with Extensive CD	Children with Limited D2 involvement
N	70	6	64	11
Female/male	47/23	4/2	43/21	5/6
Age	5.4 y (9 m-13.5 y)	5 y (3.4 – 5.1 y)	5.4 y (2.5 – 7.9 y)	3.7y (2.3-7.5 y)
Family history of CD	9(12%)	0	9(14%)	2(18%)
Clinical manifestations				
Abdominal pain	33(47%)	1(16%)	32(50%)	4(36%)
Poor weight gain or weight loss	30(42%)	0	4(6%)	2(18%)
Bone Pain	26(37%)	1(16%)	25(39%)	4(36%)
Diarrhea	18(26%)	0	18(28%)	2(18%)
Abdominal distension	17(24%)	1(16%)	16(25%)	0
Vomiting	17(24%)	0	17(26%)	3(27%)
Constipation	13(18%)	2(32%)	11(17%)	1(9%)
Short stature	11(15%)	3(50%)	8(12%)	3(27%)
Decreased appetite	4(6%)	-	4(6%)	1(9%)
Recurrent aphthous	2(3%)	0	2(3%)	0
Clubbing	2(3%)	0	2(3%)	0
Ichthyosis	1(1%)	1(16%)	0	0
Associated diseases				
Diabetes	3(4%)	1(16%)	2(1%)	0
Anemia	28(40%)	3(48%)	25(1%)	3(1%)
Hypothyroidism	2(3%)	0	2(1%)	0
Laboratory tests				
Abnormal liver function tests	7(10%)	0	7(1%)	2(1%)
Vitamin D insufficiency	29(41%)	2(32%)	27(1%)	5(1%)
Vitamin D deficiency	4(6%)	0	4(1%)	0
Mean Anti TTG-IgA(IU/ml)	184± 174	75±61	195±178	2.14±227
Anti TTG-IgA>18	70(100%)	6(100%)	64(1%)	11(1%)
Anti TTG-IgA>120	40(57%)	2(1%)	38(1%)	6(1%)
Anti TTG-IgA>300	22(31%)	0	22(1%)	3(1%)
Endoscopic Findings(normal/abnormal)				
normal appearance of D1 Abnormal appearance of D1	30(42%) 40(57%)	5(83%) 1(16%)	25(39%) 39(60%)	7 (63%) 4(36%)
normal appearance of D2 Abnormal appearance of D2	10 (15%) 60(85%)	3 (50%) 3(50%)	7 (11%) 57(89%)	2(18%) 9(81%)

CD: celiac disease, USCD: ultra-short CD, TTG IgA: tissue transglutaminase antibody immunoglobulin A, IU/ml: international unit per milliliter of blood, D1: first part of duodenum, D2: second part of duodenum

Table-2: Histopathology findings of duodenum

Marsh classification	D1	D2
0	10(14.3%)	4(5.7%)
1	1(1.4%)	2(2.9%)
2	4(5.7%)	5(7.1%)
3A	22(31.4%)	27(38.6%)
3B	15(21.4%)	14(20%)
3C	18(25.7%)	18(25.7%)

Marsh 3A was the most frequent pathology finding reported in both sites. All 6 cases in USCD group showed Marsh 3 in D1 and Marsh 0 or 1 in D2. 8 individuals (11.4%) had a higher Marsh score in D1 than in D2. Among them, six cases (8.6%) were in group 1. 53 cases had the same histology in D1 and D2 and 11 cases (15.7%) had histological changes limited to D2.

The demographic data, clinical presentation, serological values, and histopathological findings of those children with CD changes restricted to D1 are shown in **Table 3**, four cases were female and gross appearance of upper endoscopy was normal in 5 of 6 cases; but all of them had Marsh 3 in histopathology. None of the children had chronic diarrhea.

Demographic data, clinical presentations, serological values, and histopathological findings of children with CD changes restricted to D1

Table-3: Characteristics of the six patients in USCD group

Parameter	1	2	3	4	5	6
Gender	Female	Male	Female	Female	M	Female
Age	5	3.5	5	3.3	5	5.8
ANTI TTG-IGA- IgA Titer	54	151	35	54	153	31
Endoscopic appearance of D1	Cobblestone	Normal	Normal	Normal	Normal	Normal
Endoscopic appearance of D2	Normal	Scalloping	Normal	Nodularity	Scalloping	Normal
Histology of D1	3A	3A	3B	3A	3B	3A
Histology of D2	1	1	0	0	0	0
Clinical symptoms	Chronic abdominal pain, Abdominal distension, Bone pain, poor Weight gain	Chronic constipation, Ichthyosis	Chronic constipation, short stature	short stature	short stature poor Weight gain	Asymptomatic
Other characteristics	Insufficient vitamin D	Insufficient vitamin D	Insufficient vitamin D	Anemia	-	Diabetes, Anemia

4- DISCUSSION

This study provides the first comparison of disease characteristics between children with USCD and those who had extensive CD in a group of Iranian children. The results of this study showed that 64 (79%) cases had CD-related pathology (Marsh 2 or 3) in D2 with or without findings in D1 (extensive CD involvement). From these 64 patients, 53 (75.7%) cases involved D1 and D2; and 11(15.7%) patients involved just D2 segment. Our findings revealed that 6 cases (8.6%) of pediatric patients had a Marsh score of 3(A-C) in D1and Marsh 0 or 1 in D2 that represents a key role for D1 biopsy in reducing missed CD patients.

Small bowel biopsies are the cornerstone for the definitive diagnosis of CD which is based on the demonstration of characteristic histopathological changes in duodenum (10-24). It is also well recognized that histological changes in CD are patchy and hence the ESPGHAN guideline recommends multiple endoscopic biopsy samplings, including at least four biopsies from D2 and one biopsy sample from D1 (10); despite, it is unclear that how many biopsy samples are required for the diagnosis of CD (19). In the present study, we followed the method recommended in ESPGHAN guidelines and we found 6 cases with exclusive involvement in D1 (USCD) (10). Some physicians conventionally avoided taking biopsies from D1, conceding that histology of this area is slightly challenging to explicate due to the existence of shorter and broader villi in D1, Brunner's gland hyperplasia and peptic duodenitis (23-25). Also, there might be an increased risk of false-positive diagnosis, because morphological injury is common in D1 even in the absence of CD (26). To eliminate this risk, it should be noticed that some considerations such as sending D1 specimen separately, performing upper endoscopy under a gluten-containing diet to avoid false negative results, and collecting one-bite (rather than double bite) at each pass of the forceps decrease the risk of losing specimens, improve the chance of good orientation, and minimize the risk of overestimated mucosal atrophy (27). Moreover, a number of recent research studies pointed out that D1 is the only part with CD-related histologic changes (20-23). In these studies, the proportion of children with USCD ranged from 2.4% to 11.4% (11, 16, 17, 19, 20, 23, 28, 29). Interestingly, Narang et al. recently published the significant role of an additional third part of duodenum (D3) biopsy in CD diagnosis which needs more research to be better clarified (30). Most of the cases (67%) in our study were female; this is consistent with several previous reports (16, 20, 231, 31). Abdominal pain was the main clinical feature in extensive CD children, whereas short stature was the main manifestation among children with USCD. Similarly, a report from Iran showed that abdominal pain is the most common symptom among Iranian children with CD (31, 32). This finding is also supported by several reports (20, 23, 29). In 11 children (15.7%) of our cases, the mucosal involvement was limited to D2, which exhibits the patchy nature of CD. The rests (53 cases) had both D1 and D2 CD-related histology. Our results demonstrated no significant association between demographic data, clinical characteristics, associated diseases, and histological patchiness between the two groups. Similarly, Sharma et al. reported that from a total of 101 CD diagnosed children with the mean age of 8.21 years, 7.9% had CD histological changes limited to D1. In this study, there was no significant difference between clinical presentation, distribution of serological levels and histology changes between children with USCD compared with the rest of CD patients (23). Likewise, Weir et al. assessed the clinical features of 101 children with CD. The prevalence of

USCD was approximately 10%. They also revealed no clinically significant difference between groups (29). Conversely, Doyev et al. reported in their large study that among 648 children with the mean age of 6.5 years, 71 (11%) cases had USCD. Children in USCD group had lower rates of diarrhea, anemia and milder histopathological changes at presentation compared with the extensive group (20). Mooney et al. conducted a research on 268 CD diagnosed adult cases (mean age: 50.3years). 9.7% of the cases had exclusive bulb involvement. They demonstrated that adult patients with USCD had lower prevalence of diarrhea and infrequent nutritional deficiencies, compared to other CD patients (22). The possible explanation for milder disease phenotype among patients with USCD reported by Doyev (2018) and Mooney (2016) might be related to the extent of the disease (20, 22). Of course, a short segment of villous atrophy causes less loss of absorptive capacity and limited symptoms. This might also explain the short duration of disease as well as the diagnosis of CD at an earlier stage; however, in our study, there was no significant difference between the two groups in terms of clinical symptoms. Although, 8 cases in our study had higher Marsh scores in D1 than in D2, emphasizing the importance of separate and multiple D1 samples at the time of upper endoscopy. Our study revealed Marsh 3A as the most frequent pathology finding in both sites. One study has shown that titer of anti-TTG antibody was 10 times greater than the upper limit of normal. This is significantly associated with Marsh grades greater than two (33). We also found that 35 /40 cases with Anti-TTG IgA levels more than 10 times higher than the upper normal limit had Marsh grade 3 in at least one site, although none of these children belonged to group 1. We perceived that the mean Anti TTG-IgA level in patients with USCD was lower than patients with extensive CD (P= 0.11). Some studies also reported lower anti-TTG IgA levels at diagnosis in USCD adults and children, respectively (20, 22). Doyev et al. considered that this may be explained by limited extents of bowel involvement. Moreover, antibody production is a time consuming process and antibody level can increase with time in parallel with disease extent (20). It seems possible that the first segment to be reached by dietary gluten epitopes is D1 and then progresses to distal parts of duodenum (34). Moreover, low-titres of antibodies in USCD and mild-enteropathy CD could miss diagnosis made by a serology-based diagnostic strategy (26). In spite of reports which emphasized on the important role of D1 biopsies in CD diagnosis, Ravelli et al., in 110 children with CD, found no cases with limited D1 involvement (35).

New research demonstrated that USCD patients showed different genetic and immuno-phenotypic characteristics compared to conventional CD including lower presence of the DQ2 haplotype, plus less levels of TTG-IgA and duodenal NK cell suppression (36). Also, usage of new tools can help improve diagnosis of CD in early phases including double immunohistochemistry which showed Intestinal transglutaminase (TG2) IgA deposits in all children with overt celiac disease (37). Also, in other research, pan-gastrointestinal mucosal biopsies revealed evidence of lymphocytic infiltration and IgA anti-TTG deposits along the gastrointestinal tract suggesting that gastrointestinal tract involvement may be beyond the small intestine (38). Utility of these methods in future research may have a significant role in the diagnostic yield for celiac disease and reduce the potential for long term sequelae of celiac disease such as lymphoma and/or osteoporosis (39).

4-1. Limitations of the study

Our research had some limitations. First, this study was conducted in a single

tertiary center with a small sample size. The next limitation is the incomplete availability of laboratory results and, especially, anti-EMA that was not available in our region. For future investigations, we recommend a multicenter study with larger sample sizes in this topic.

5- CONCLUSION

This study revealed that small but clinically significant number of patients with pathological changes restricted to the duodenal bulb (6 cases, % 8.6) emphasizing the importance of the adherence to guideline recommendations for taking both duodenal bulb and second part of duodenum biopsies in separate containers for correct diagnosis of CD and better CD case finding.

6- ETHICAL CONSIDERATIONS

Informed consent was obtained from all subjects using protocols approved by the Ethics Committee of the Mashhad University of Medical Science (IR.MUMS.MEDICAL.REC.1398085).

7- AVAILABILITY OF DATA AND MATERIALS

The data that support the findings of this study are available from the corresponding author upon reasonable request.

8- CONFLICTS OF INTEREST

The authors declare no conflict of interest.

9- FUNDING

There is no funding in this study.

10- AUTHORS' CONTRIBUTIONS

We declare that we contributed significantly towards the research study; SAJ and TS conceptualized and administered the project. YAM, AAM and SAJ performed the investigation. FB wrote the original draft. MKR and SI carried out the data analysis. All authors reviewed and approved the manuscript.

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