Original article:

Investigation of celiac disease according to Marsh classification in childhood

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Abstract

Background: Celiac disease (CD) is an autoimmune disorder of the small intestine related to gluten. CD is diagnosed by the evaluation of histologic findings according to the Marsh classification. **Objectives:** To evaluate the clinical and laboratory differences of CD according to Marsh classification. ***Patients and method:*** The records of ≥Marsh 2 histologically diagnosed 132 cases were evaluated. ***Results:*** It was determined that 7(5.3%) cases were Marsh 2, 32(24.2%) were Marsh 3a, 73(55.3%) were Marsh 3b, and 20(15.1%) were Marsh 3c. Vomiting in Marsh 2 was significantly lower than Marsh 3b and Marsh 3c (respectively, 14.3% vs. 56.9%, p=0.029; and 14.3% vs. 75%, p=0.005). Hemoglobin was significantly higher in Marsh 2 than Marsh 3b and Marsh 3c (respectively, 11.9±1.7 vs. 10.5±1.6 g/dl, p=0.038 and; 11.9±1.7 vs. 9.8±1.6 g/dl, p=0.005). Positive detection ratio for tTG IgA was significantly lower in Marsh 2 than Marsh 3a, Marsh 3b and Marsh 3c (respectively, 66.7% vs. 100%, p<0.001; 66.7% vs. 100%, p<0.001; and 66.7% vs. 94.1%, p=0.003). After the onset of gluten free diet, the time passed for the disappearance of tTG IgA seropositivity is significantly shorter in Marsh 2 than Marsh 3c (6±3.6 vs. 9.7±2.5 months, p=0.017). ***Conclusions:*** Gastrointestinal symptoms are more frequent in patients with severe small intestinal mucosal injury. tTG IgA seropositivity is associated with more severe disease. Clinical and laboratory findings of the patients are exacerbated when histopathological findings improve in CD.

Keywords: Celiac disease; Marsh classification; serological tests; children

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Introduction

Celiac disease (CD) is a multi-systemic, autoimmune disease that develops as a result of an interaction between genetic and environmental factors. The most important characteristics of the disease are villous atrophy and malabsorption that develop in the intestinal system after ingestion of gluten-containing food.[1] A definite diagnosis of the disease is made based on a biopsy of the small bowel. Serological tests are mostly used for screening purposes.[2] Notably, five to seven cases are pending for diagnosis for every diagnosed case, even though our knowledge and diagnostic methods have improved.[3] Finland has the highest rate of CD in Europe at 2.4%. The lowest rate is 0.3% in Germany and the average rate is 1%.[4] Rates reported in Turkey range from 0.6%[5] to 1.3%.[6] CD causes basically three clinical conditions such as classical, atypical and asymptomatic forms. Nonetheless, it causes growth retardation,[7] autoimmune diseases[8] and malignancies.[9] Preventing these consequences depends on early diagnosis and treatment of the disease. CD is diagnosed on the presence of the following elementary lesions: increased intraepithelial T lymphocytes, crypt hyperplasia and villous atrophy (mild, moderate and total) and classified according to the Marsh classification.[10] We could not identify any study about the relationship between CD findings and Marsh

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classification in the literature. In this study, we aimed to investigate the clinical and laboratory differences of CD according to Marsh classification.

Material and Methods

The retrospective study commenced after approval was received from the local board of ethics. The records of all children who were followed up for a celiac disease diagnosis between 2007 and 2012 in the Department of Pediatrics, Abant Izzet Baysal University Faculty of Medicine, and the Department of Pediatric Gastroenterology, Hepatology and Nutrition, Dortcelik Children's Hospital were retrospectively examined. Demographic characteristics of the patients, their symptoms at presentation, physical examination findings, laboratory parameters (complete blood count, blood biochemistry values, liver function tests, and zinc levels), serological studies (anti-gliadin antibody (AGA), anti-endomysium antibody (EMA), tissue transglutaminase antibody (tTG)) results were recorded. AGA and tTG were checked using an enzyme-linked immunosorbent assay, while EMA was evaluated using the immunofluorescent method. The typical intestinal signs were consisted of diarrhea, abdominal pain, abdominal distension and, vomiting. The atypical extra-intestinal signs were consisted of delayed puberty, edema and rickets. Biopsy material was collected from the second part of the duodenum and assessed by pathologists. The diagnosis of disease was based on the presence of the following elementary lesions: increased intraepithelial T lymphocytes, crypt hyperplasia and villous atrophy (mild, moderate and total) and classified according to the Marsh classification.[10] The patients were divided into groups according to form of disease and Marsh classification.

The statistical analysis was conducted using SPSS 15.0 software (SPSS, Inc., Chicago, IL, USA). The Student's t, One-way Anova, Kruskal–Wallis and the Mann–Whitney *U*-tests were used for the comparisons. A $p < 0.05$ was considered significant.

Results

Totally 132 cases with biopsy proven CD were included in this study. Eighty cases were female (60.6%), but the difference between the sexes was not significant. Median age was 8 years (range, 1–17 years). The median age at diagnosis was 60 months (range, 7 months–192 months). The median value for the duration between the development of clinical symptoms and the definitive diagnosis was 12 months (range, 1–132 months).

A total of 51 of 60 (85%) cases were positive for AGA IgA or IgG; 57 of 64 (89%) cases were positive for EMA IgA or IgG and 81 of 82 (98.7%) cases were positive for tTG IgA or IgG. After the onset of gluten free diet, the disappearance of tTG IgA seropositivity took 8.3±3 months. Anemia was identified in 62 (46.9%) cases; transaminases were high in 15 (11.3%) cases.

Two (1.3%) had type-1 diabetes mellitus, one (0.6%) had IgA deficiency, four (2.6%) had autoimmune thyroiditis. A total of 15 (9.8%) of the cases had a family history of CD.

Patients were evaluated according to gender (Table 1). Male patients were at lower age (7.5±4.8 vs. 9.3±4.4 years, p=0.035), diagnosed earlier (53.4±44.6 vs. 79.4±56.5 months, p=0.005), shorter duration between onset of symptoms and diagnosis (15±22.1 vs. 20.3±22.5 months, p=0.027). Diarrhea was higher among males (80.3 vs. 58.7%, p=0.01) while constipation was higher among females at presentation (16.6 vs. 4%, p=0.033). Likewise, ALT (74.6±256 vs. 29.4±28.8 IU/L, p=0.044) was significantly higher in males. No significant differences were found for the other parameters (p>0.05).

Patients were evaluated according to clinical form (Table 2). Age and the age at the diagnosis of patients in classical CD was lower than atypical and asymptomatic forms (respectively, 7.8±4.4 vs. 14.8±3.1 years, p<0.001; and 7.8±4.4 vs. 12.2±1.8 years, p=0.016) and (respectively, 61.2±49.1 vs. 133.2±49.7 months, p<0.001; and 61.2±49.1 vs. 130±40.1 months, p=0.003). Chronic diarrhea was more common in classical CD than atypical form (74.8 vs. 20%, p<0.001). However, tooth enemal defect was less common in classical CD than atypical form (9.2% vs. 60%, p<0.001). Positive detection ratio for tTG IgA was significantly lower in atypical form than classical and asymptomatic forms (respectively, 83.3% vs. 100%, p=0.001; 83.3% vs. 100%, p=0.001). ALT levels were significantly higher in classical form than and atypical forms (53±178.6 vs. 16.2±6.3 IU/l, p=0.047). Serum zinc levels were significantly higher in asymptomatic form than classical and atypical forms (respectively, 99.4±31.1 vs. 54.4±35.9 µg/dl, p=0.007; and 99.4±31.1 vs. 55.7±36.4 µg/dl, p=0.028). No significant differences were found for the other parameters (p>0.05).

As a result of the pathological assessments, it was determined that 7 (5.3%) cases were Marsh 2, 32 (24.2%) cases were Marsh 3a, 73 (55.3%) cases were Marsh 3b, and 20 (15.1%) cases were Marsh 3c (Table 3). The age of patients in Marsh 2 were significantly higher than Marsh 3a, Marsh 3b and Marsh 3c (respectively, 13.1±3.8 vs. 8.1±4.7 years,

p=0.01; 13.1±3.8 vs. 9±4.6 years, p=0.024; and 13.1±3.8 vs. 6.3±4.1 years, p=0.001). The age of patients at diagnosis in Marsh 2 were significantly higher than Marsh 3a, Marsh 3b and Marsh 3c (respectively, 142.2±51.6 vs. 63.5±49.7 months, p<0.001; 142.2±51.6 vs. 69.2±53.3 months, p<0.001; and 142.2±51.6 vs. 59±47.5 months, p<0.001). The weight of patients in Marsh 2 were significantly higher than Marsh 3a, Marsh 3b and Marsh 3c (respectively, 33±13 vs. 18.6±10 kg, p=0.009; 33±13 vs. 20.4±14.5 kg, p=0.015 and; 33±13 vs. 15.9±10 kg, p=0.003). Vomiting in Marsh 2 was less common than Marsh 3b and Marsh 3c (respectively, 14.3% vs. 56.9%, p=0.029; and 14.3% vs. 75%, p=0.005). Hemoglobin was significantly higher in Marsh 2 than Marsh 3b and Marsh 3c (respectively, 11.9±1.7 vs. 10.5±1.6 g/dl, p=0.038 and; 11.9±1.7 vs. 9.8±1.6 g/dl, p=0.005). Positive detection ratio for tTG IgA was significantly lower in Marsh 2 than Marsh 3a, Marsh 3b and Marsh 3c (respectively, 66.7% vs. 100%, p<0.001; 66.7% vs. 100%, p<0.001; and 66.7% vs. 94.1%, p=0.003). Autoimmune thyroiditis was more common in Marsh 3c than Marsh 3a and Marsh 3b (respectively, 25 vs. 6.2%, p=0.044; and 25 vs. 0%, p=0.003).After the onset of gluten free diet, the time passed for the disappearance of tTG IgA seropositivity is significantly shorter in patients with Marsh 2 than patients with Marsh 3c (6±3.6 vs. 9.7±2.5 months, p=0.017). No significant differences were found for the other parameters (p>0.05).

Discussion

Recent studies have changed our perceptions of CD. One of the most important updates is that it is not a simple malabsorption disease, but a complex ailment involving several systems.[3] Therefore; it is difficult to identify its actual prevalence. Thus, CD is considered in the differential diagnosis of many conditions with no clearly identified etiologies.[11]

CD has the same rate of incidence in both gender as in our study,[12] but there are publications suggesting that the majority of celiac patients are female.[13,14] The reason of female predominance is unknown, but it could possibly be related to immune-mediated diseases usually which are more frequent in females.[15]

The initiation of complaints of celiac disease may vary among populations depending on genetic and environmental factors such as breastfeeding duration, the age of encounters with gluten, amount of gluten consumed, and past viral infections.[16] The timing of added gluten into the diet is the most important factor. If gluten is started before 3rd months of life, complaints begin quickly. However, gluten initiated after 7th months increases the risk of CD in later life.[17] The ages at which patients are diagnosed ranges from 5.1[18] to 9.3[14] years. Our study results were consistent with the literature.

CD is a food allergy that continues throughout life. Once the disease is diagnosed, patients must change their way of life not only to eliminate their symptoms but also to prevent any potential complications.[19]

Different serological tests have been used to screen the celiac disease. These tests are used to search for antibodies formed against gluten and the structural proteins in the intestinal mucosa.[20] These antibodies are formed from the IgA structure and in the weaker IgG structure. The transglutaminase enzyme, which exists in many organs but especially in the small intestine, is the most important target for these auto-antibodies. The antibody developed against this protein is the preferred serological markers for celiac disease.[21] The positive ratios on the serological tests used in the present study (AGA, EMA, and tTG) were 85%, 89%, and 98.7%, respectively. Some studies have stated that diagnostic value of tTG and EMA were high while AGA was low.[22,23] tTG which is directly associated with tissue damage is used for the prediction of the development of villous atrophy, and the disappearance of the disease after initiating gluten-free diet.[24]

tTG IgA seropositivity is also used for follow-up, to confirm patients compliance with their gluten-free diet, as well as for screening of the disease.[25] The disappearance of this antibody is significant for showing the repair of damaged intestinal mucosa in most of the patients.[26] After the onset of gluten free diet, the disappearance of tTG IgA seropositivity takes 8.3±3 months in our study. This information indicates that our patients didn't comply enough with their diet.

CD is a malabsorption disease, therefore, patients often present with chronic diarrhea, vomiting, abdominal pain and abdominal distension.[14,27] These complaints are often seen in classical CD and it is the most common form of the disease as in our study.[13,14,27] On the other hand, there are some publications reported that atypical form is more frequent.[28,29]

Some individuals with CD may present with anemia. Anemia usually occurs due to impaired absorption of iron, foliate, and vitamin B12 caused by mucosal damage.[30] Especially iron-deficiency anemia that is unresponsive to therapy should alert the physician for the diagnosis of CD in the absence of any symptom. The prevalence of anemia is between 34-55% in CD.[25,28] The rate that we found is consistent with the literature. Anemia was determined more commonly in patients admitted with atypical form.[31] Conversely,

Kuloglu et al[32] reported that anemia is seen more in classical form. However, we did not found any association between form of CD and anemia.

Hypertransaminasemia is an important laboratory finding in CD. The reason of this pathology is unknown.[33] The prevalence of hypertransaminasemia is between 16-29%.[25,28] Deterioration in liver function tests is observed in classical form of CD as in our study.[32,34] Children with unexplained hypertransaminasemia should be evaluated for CD.[32]

Tooth enamel defects are more common in atypical form of CD. This finding should alert the physician for the diagnosis of CD in the absence of any GI symptom, at-risk subjects.[35]

CD is closely related to autoimmune diseases.[33] The immune response, which develops when genetically predisposed individuals encounter gluten, may cause the emergence of some autoimmune diseases in addition to villus destruction.[36] The most frequently detected pathology was autoimmune thyroiditis as in our study.[33] Thyroid gland diseases dominated in atypical celiac disease,[34] but we did not observe any relation between these two matters in our study.

Zinc deficiency is a laboratory finding of CD and it is developing due to endogenous losses or abnormal zinc absorption.[37] Growth retardation also occurs in zinc deficiency in CD as in present study.[38] We found that serum zinc level is the most reducing one in classical CD.

There is a publication claims that GI symptoms are more common in male while the other claims that there is not any difference among males and females according to GI symptoms.[12,13] We found a significant correlation between gender and GI symptoms in present study. CD is early diagnosed in male due to findings such as chronic diarrhea and hypertransaminasemia. Additionally, female with CD may present with complaint of constipation as in our study.[39]

We found that in celiac patients with major injury in small intestinal mucosa, GI symptom such as vomiting is more common. Malabsorption occurring due to the damage of the GI tract leads to growth retardation and anemia in these patients. Whereas, Ehsani-Ardakani et al[13] reported that there is not any relation between GI symptoms and the type of Marsh histopathology.

We found a significant association between injury in small intestinal mucosa and tTG IgA seropositivity. tTG IgA seropositivity points out a more severe disease in histopathological evaluation. Vivas et al[40] reported that highly elevated levels of tTG is closely related with villous atrophy. Nonetheless, with the increased severity in injury of small intestinal mucosa, the time passed for the disappearance of tTG IgA seropositivity elongates.

Conclusion

The majority of the patients were females but we noticed that, males expressed more profound and striking clinical conditions and diagnosed earlier than females. Hypertransaminasemia is more evident in classical CD. GI symptoms are more frequent in patients with severe small intestinal mucosal injury. tTG IgA seropositivity is associated with more severe disease. Clinical and laboratory findings of the patients are exacerbated when histopathological findings improve in CD.

Acknowledgment

Competing interests: The authors declare that they have no competing interests in relation to this manuscript.

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Table 1: Comparison of the characteristics of patients sorted by gender

Variables	Male (n=52)	Female (n=80)	p
Age (Y)[1]	7.5±4.8	9.3±4.4	0.035
Age at diagnosis (M)[1]	53.4±44.6	79.4±56.5	0.005
Duration between symptoms&diagnosis (M)[1]	15±22.1	20.3±22.5	0.027
Chronic diarrhea[2]	41 (80.3)	47 (58.7)	0.01
Constipation[2]	2 (4)	13 (16.6)	0.033
AST (IU/L)[1]	148.6±695.3	36.7±18.5	0.056
ALT (IU/L)[1]	74.6±256	29.4±28.8	0.044

([1]:Mean±SD, [2]:n (%),Y:Years, M:Months)

Table 3: Characteristics of patients according to Marsh classification

Variables	Marsh 2 (a) (n=7)	Marsh 3a (b) (n=32)	Marsh 3b (c) (n=73)	Marsh 3c (d) (n=20)	p
Age (Y)[1]	13.1±3.8	8.1±4.7	9±4.6	6.3±4.1	0.01[a-b], 0.024[a-c], 0.001[a-d]
Gender (M/F)[2]	1/7	14/32	29/73	8/20	0.55
Age at diagnosis (Y)[1]	142.2±51.6	63.5±49.7	69.2±53.3	59±47.5	<0.001[a-b], <0.001[a-c], <0.001[a-d]
Duration between symptoms& diagnosis(M)[1]	19.8±14.4	24.3±33.7	16.6±18.7	17.4±18.5	0.47
Weight (kg)[1]	33±13	18.6±10	20.4±14.5	15.9±10	0.009[a-b], 0.015[a-c], 0.003[a-d]
Height (cm)[1]	123±28	113±31	109±27	113±28	0.59
Abdominal distension[2]	3 (42.9%)	20 (62.5%)	51 (70%)	17 (85%)	0.15
Chronic diarrhea[2]	4 (57.1%)	22 (68.8%)	46 (63%)	17 (85%)	0.28
Abdominal pain[2]	3 (42.9%)	25 (78.1%)	55 (76.4%)	15 (75%)	0.25
Vomiting[2]	1 (14.3%)	13 (41.9%)	41 (56.9%)	15 (75%)	0.029[a-c], 0.005[a-d]
Edema[2]	0	3 (9.7%)	3 (4.2%)	2 (11.1%)	0.5
Puberte tarda[2]	2 (28.6%)	3 (9.7%)	8 (11.1%)	2 (11.1%)	0.65
Rickets[2]	1 (25%)	6 (24%)	10 (17.2%)	0	0.24
Tooth enamel defect[2]	2 (50%)	3 (12.5%)	9 (15%)	0	0.081
Hemoglobin (g/dl)[1]	11.9±1.7	10.7±1.3	10.5±1.6	9.8±1.6	0.038[a-c], 0.005[a-d]
Hematocrit[1]	36±5.1	32.6±3.9	31.8±4.9	30.3±5.2	0.085
AST (IU/L)[1]	45.6±31	43.6±29.1	113±589,3	39.6±16.9	0.9
ALT (IU/L)[1]	45.3±37.8	36.4±38.7	58.2±217.7	33.2±20.1	0.93
GGT (IU/L)[1]	12±3	14.6±11.1	15±12.8	10.2±2.5	0.54
Total biluribin (mg/dl)[1]	6.7±0.8	6.7±0.6	6.6±0.9	6.8±0.9	0.84
Albumin (mg/dl)[1]	3.7±0.5	3.9±0.5	3.9±0.6	3.9±0.6	0.97
IgA (mg/dl)[1]	151.2±21.9	117.1±39.6	114.6±53.9	96.1±30.1	0.075
AGA IgA[2]	1 (100%)	12 (85.7%)	33 (84.6%)	5 (83.3%)	0.97
AGA IgG[2]	1 (100%)	12 (85.7%)	32 (84.2%)	5 (83.3%)	0.97
EMA IgA[2]	2 (100%)	11 (100%)	36 (97.3%)	8 (88.9%)	0.55
EMA IgG[2]	3 (100%)	11 (100%)	39 (95.1%)	9 (90%)	0.72
tTG IgA[2]	2 (66.7%)	19 (100%)	43 (100%)	16(94.1%)	<0.001[a-b], <0.001[a-c], 0.003[a-d]
tTG IgG[2]	3 (100%)	17 (89.5%)	38 (95%)	16(94.1%)	0.83
IDDM[2]	0	1 (4.5%)	1 (1.8%)	0	0.81
Familial history[2]	1 (50%)	6 (28.6%)	7 (12.5%)	1 (10%)	0.19
Autoimmune thyroiditis[2]	1 (50%)	1 (6.2%)	0	2 (25%)	0.003[c-d], 0.044[b-d]
Serum zinc (µg/dl)[1]	66.7±34.1	60.3±32.2	55.6±39.3	47.8±33.7	0.61
Form of disease (C/At/As)[2]	5/1/1	29/1/2	63/7/3	19/1/0	0.68
Disappearance of tTG IgA[1] (M)	6±3.6	8.2±2.5	8.2±3.2	9.7±2.5	0.017[a-d]

([1]:Mean±SD, [2]:n,Y:Years, M:Months)

Table 2: Characteristics of patients according to clinical form of CD

Variables	Classical (n=115)(a)	Atypical (n=11) (b)	Asymptomatic (n=6) (c)	p
Age (Y)[1]	7.8±4.4	14.8±3.1	12.2±1.8	<0.001 [a-b], 0.016[a-c]
Age at diagnosis(M)[1]	61.2±49.1	133.2±49.7	130±40.1	<0.001 [a-b], 0.003[a-c]
Weight (kg) [1]	17.8±11.6	29.5±13.6	39.5±14.3	0.004 [a-b], <0.001[a-c]
Chronic diarrhea[2]	86 (74.8%)	2 (20%)	0	<0.001 [a-b]
Tooth enamel defect[2]	8 (9.2%)	6 (60%)	0	<0.001 [a-b]
ALT[1]	53±178.6	16.2±6.3	18±9.8	0.047[a-b]
tTG IgA[2]	75 (100%)	5 (83.3%)	2 (100%)	0.001[a-b], 0.001[b-c]
Serum zinc[1]	54.4±35.9	55.7±36.4	99.4±31.1	0.007 [a-c], 0.028[b-c]

([1]:Mean±SD, [2]:n (%),Y:Years, M:Months)

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