Original Article

Clinical Spectrum of Celiac Disease in Children in Sistan and Baluchestan Province

Touran Shahraki MD•[1,2], Ivor D. Hill MD[3]

Abstract

Background: The clinical manifestations of celiac disease (CD) have changed in the past decades. There are currently little data describing the initial clinical manifestations of CD in children in Iran. This study describes the initial presentation of children with suspected CD from a geographically defined region in Iran.

Method: Medical records of children seen in 2007 – 2015 from Sistan and Baluchestan province, Iran, with suspected CD were reviewed. After obtaining TTG-IgA and IgA, subjects were divided into three groups according to presenting symptoms: GI, non-GI, and asymptomatic group. Those with elevated TTG-IgA or a strong clinical suspicion for CD underwent endoscopy with duodenal biopsy. Demographic data, symptoms, laboratory, histopathology findings and the presence of any CD related conditions were recorded.

Results: from 344 children who underwent upper endoscopy and intestinal biopsy, 105 cases with marsh 0 – 1 were excluded from the study and 239 cases considered as a definite celiac disease (Mean± SD of age was 6.8 ± 3.9 years with 145 females). GI symptoms were predominant in the younger age groups while non-GI symptoms were more common in the older children. The most frequent GI and Non-GI symptoms were abdominal pain (41.4%), distension (36.4%), diarrhea (32.2%), under nutrition (51.4%), anemia (36.4%), and decreased bone age (35%). The most common co-morbidities were hypothyroidism (3.7%) and Type 1 diabetes (2.9%).

Conclusion: GI complaints in Iranian children are a common feature. Screening of children with suspected CD, especially with GI symptom is highly recommended.

Keywords: Celiac disease, children, disease, Iran

Cite this article as: Shahraki T, Hill ID. Clinical spectrum of celiac disease in children in Sistan and Baluchestan province. 2016; **19(11):** 762 – 767.

Introduction

Celiac disease (CD) is an immune-mediated systemic disorder elicited by ingestion of gluten and related prolamines in genetically susceptible individuals.[1] It is a common disorder, with an estimated prevalence of 0.5% to 1% of the general population in most European countries.[2]

The availability of sensitive and specific serological tests has changed the epidemiology of CD from a rare disease to a frequent condition not only in Europe, but also in developing countries.[3] Studies from Iran have shown the prevalence of CD to be 0.5% – 0.6% among healthy Iranian school-age children [4,5] Nonetheless, the majority of patients with CD may remain undiagnosed due to iceberg pattern in celiac disease.[6]

CD has a wide range of presenting manifestations. Based on the clinical presentation, CD can be categorized as having gastrointestinal or non-gastrointestinal symptoms. In addition, there are known asymptomatic cases identified on the basis of a positive serology test and subsequent intestinal biopsy. Although the classical (typical) form of CD is characterized by chronic diarrhea, failure to thrive (FTT) and abdominal distention starting between 6 and 24 months of age, recent publications have demonstrated that during the past several decades this presentation is now less common. Nowadays children are more likely to present with digestive complaints such as recurrent abdominal pain, nausea, vomiting, and constipation or extra digestive manifestations, including short stature, iron deficiency anemia (IDA), osteopenia and abnormalities in liver function tests.[7–9] A greater awareness of the variable manifestations of CD, and more liberal use of serologic tests is needed to identify more cases in a timely manner.

There is little published data on the clinical spectrum of CD in Iran. The aim of this study was to describe the initial presentation of children and adolescents with suspected CD from a geographically defined region in Iran.

Method

During the period 2007 – 2015, a total of 507 children with suspected CD underwent testing for serum TTG IgA antibody and serum IgA levels. Presenting clinical manifestations included GI symptoms (chronic diarrhea, chronic abdominal pain, bloating and constipation) or extra-intestinal manifestations (FTT, IDA, increased level of liver enzymes and short stature). In addition, asymptomatic subjects belonging to groups at increased risk for CD (e.g. first degree relatives) were included. Of these, 344 cases underwent an upper GI endoscopy with small intestinal biopsy.

The study was undertaken in Ali-Asghar Hospital in Zahedan, Iran, which is the only referral pediatric GI clinic in the entire Sistan and Baluchestan province (The province is the largest in

Authors' affiliations: [1]Department of Pediatrics, Division of Pediatric Gastroenterology, Zahedan University of Medical Sciences, Zahedan, Iran, [2]Research Center for Children and Adolescent Health, Zahedan, Iran, [3]Division of Pediatric Gastroenterology, Nationwide Children's Hospital, Columbus, Ohio, USA.

•Corresponding author and reprints: Touran Shahraki MD, Department of Pediatrics, Faculty of Medicine, Zahedan University of Medical Sciences, Research Center for Children and Adolescent Health, Zahedan, I. R. of Iran. Tel: 98-915-3413960, Fax: 98-54-33447092, E-mail: Dr_tshahraki@yahoo.com.

Accepted for publication: 7 September 2016

Iran, with an area of 181,785 km² and a population of 2.5 million with 15 cities and located at the south east of Iran).

Written informed consent was obtained from the parents or legal guardians in all children undergoing endoscopy and biopsy. The study was approved by the Ethics Committee of the Zahedan Medical University of Sciences and Research Center for Children and Adolescent Health.

Data on each patient was extracted from the medical records. This included demographic characteristics, growth indices, presenting symptoms and signs and the presence of associated conditions such as type 1 diabetes. Laboratory data collected included a CBC, Serum IgA, TTG IgA, liver function tests and Marsh histology score. TTG IgA and total IgA were checked by commercial ELISA kit (AESKULISA, GERMANY) and Bionik-immunoturbidimetric Assay, England, respectively. TTG IgA titers of <=12 U/ml were taken as negative, 12-18 U/ml as borderline and =>18U/ml as positive. In cases with IgA deficiency, a serological test for and TTG-IgG was requested. Biopsies were obtained during upper GI endoscopy and graded using modified Marsh classification.[10]

Diagnosis of CD was confirmed by positive serologic tests together with characteristic changes of CD on small intestinal histology and response to a gluten free diet.[11] Subjects with Marsh 2 or 3 lesions were considered as definite CD. Patients with positive TTG but without histological abnormalities in duodenal biopsies were excluded from the study.

The subjects were divided into three groups according to their primary initial presenting symptoms: GI, non-GI and silent (asymptomatic) group. Children were divided into four age groups as: < 2 years, 2 – 6 years, 6 – 10 years, and > 10 years. Under nutrition, stunting and anemia were defined based on WHO criteria and Hematologic reference, respectively.[12,13] Bone age was detected by checking wrist-X ray.

Statistical Analysis

Data were analyzed by descriptive analysis using SPSS.18 (Chicago, SPSS Inc). The Chi-square test was used to compare categorical data. The ANOVA tests were used to test the relation between age, groups and Marsh classification. The significance level was defined as $P < 0.05$.

Results

Of the 344 children who underwent upper endoscopy and intestinal biopsy, 105 cases with marsh 0 – 1 excluded from the study and 239 cases considered as a definite celiac disease (145 (61%) were female with a mean ± SD age of 6.8 ± 3.9 years (range, 0.5 – 18 years). The distribution of patients has demonstrated in Figure 1.

Of 181 (75.7%) cases presented with GI manifestation, 43 (18%) had non-GI symptoms and 15 (6.3%) cases were asymptomatic. Details of demographic data, clinical manifestations and laboratory findings for the children in each group are shown in Table 1. The most frequent GI symptoms were recurrent abdominal pain (RAP) in 99 (41.4%) followed by abdominal distension in 87(36.4%), diarrhea in 77 (32.2%), nausea /vomiting in 51 (21.3%) and constipation in 44 (18.4%). Among the extra-intestinal manifestations, under nutrition in 123 (51.4%), anemia in 87 (36.4%), decreased bone age in 84 (35.1%), and stunting in 74 (30.9%) were the most common presentations. Z score weight for age was below -2 in 123/239 patients (51.5%); of these, 59 cases (24.6%) had weight for age < -3 (severe under nutrition). Of 206 cases that had their height documented in the chart, 74 (31%) had stunting (Z score < -2). In addition, one case was overweight. A family history of CD was present in 22/239 of the cases. The most common associated co morbidities were hypothyroidism in 9 (3.7%) and diabetes Type 1 in 7 (2.9%).

Distribution of the clinical presentation according to age groups showed some significant differences (Tables 2 and 3). GI symptoms were predominant in the younger age groups while non-GI symptoms were more common in the older children. Also, the mean ± SD of age according to the presenting group and Marsh classification was analyzed (Table 3). The ANOVA test showed significant differences between groups with mean ± SD of age. The LSD post hoc test showed that patients presenting with GI symptoms were significantly younger than the other two groups ($P = 0.001$). However, there was no significant difference between age and grade of marsh ($P = 0.36$).

Histopathology evaluation revealed Marsh 3, 2, 1 and 0 in 204, 35, 72 and 33 patients, respectively. A total of 239 cases (69.4%) had a definite diagnosis of CD (marsh 2, 3) with predominance in

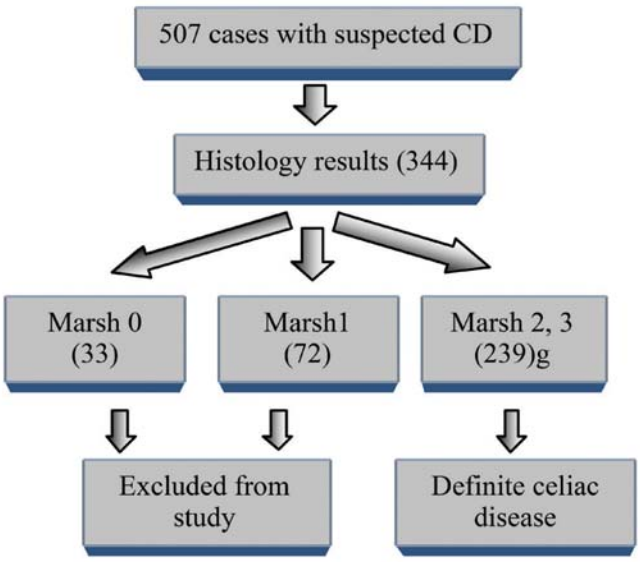

Figure 1. Flow chart of study group with suspected celiac disease

Table 1. Characteristics of 239 patients with definite diagnosis of CD

Variable	GI, N (%)	Non- GI, N (%)	Silent, N (%)	Total
Under-nutrition	91 (74)	29 (24)	3 (2.4)	123
Stunting*	50 (68)	23 (31)	1 (1.4)	74
Diarrhea	75 (97)	2 (2.6)	- - -	77
Constipation	37 (84)	7 (16)	- - -	44
Abdominal pain	88 (89)	11 (11)	- - -	99
Steatorrhea	34 (100)	- - -	- - -	34
Distention	82 (94)	5 (6)	- - -	87
Nausea/vomit	46 (90)	5 (10)	- - -	51
Rickets	1 (100)	- - -	- - -	1
Clubbing	26 (90)	1 (3.4)	2 (7)	29
Edema	9 (90)	1 (10)	- - -	10
Short stature	- - -	21 (100%)	- - -	21
Aphtosis/kelosis	8 (80)	2 (20)	- - -	10
Anemia	64 (74)	19 (22)	4 (5)	87
Low bone age**	53 (63.1)	25 (29.8)	6 (7.1)	84
Sgpt impairment	15 (75)	4 (20)	- - -	19
Family Hx of CD	12 (54)	1 (4.5)	9 (41)	22
Diabetes	3 (43)	- - -	4 (57)	7
Hypothyroidism	5 (56)	1 (11)	3 (33)	9
IgA deficiency	6 (86)	1 (14)	- - -	7
Down syndrome	4 (67)	- - -	2 (33)	6
Turner syndrome	1 (100)	- - -	- - -	1
Cirrhosis / AIH	- - -	2 (100)	- - -	2
Cystic fibrosis	1 (100)	- - -	- - -	1
nephrolitiasis	5 (83)	1 (17)	- - -	6

*,** Data were available in 206 and 145/239 cases, respectively.

Table 2. Clinical Presentation of subjects according to age groups

Age	Group (N%)			Total	*P*-value
	GI	NON GI	Silent		
< 2 years	42 (97.7)	1 (2.3)	- - -	43	0.001
2 – 6years	62 (84.9)	7 (9.6)	4 (5.5)	73	
6 – 10	54 (73)	15 (20.3)	5 (6.8)	74	
> 10 years	23 (46.9)	20 (40.8)	6 (12.2)	49	
Total	**181**	**43**	**15**	**239**	

Table 3. The mean and standard deviation, maximum and minimum of age according to group and Marsh classification

	Mean ± SD of age	*P*-value
Group		0.001*
GI (N =181)[A]	5.9 ± 3.7	
NON GI (N = 43)[B]	9.8 ± 3.4	
Silent (N = 15)[C]	8.3 ± 3.9	
Marsh		0.3**
Grade II 35	6.2 ± 3.4	
Grade III204	6.9 ± 4.0	

*Differences was significant between groups A with B and A with C; **Differences was not significant between Marsh and age.

Table 4. Clinical Presentation of subjects by marsh classification

Group	Pathology, N (%)				*P*-value
	Marsh 0	Marsh I	Marsh II	Marsh III	
GI	28 (11.2)	41 (16.4)	27 (10.8)	154 (61.6)	0.006
NON GI	4 (5.7)	23 (32.9)	6 (8.6)	37 (52.9)	
Silent	1 (4.2)	8 (33.3)	2 (8.3)	13 (54.2)	
Total	**33**	**72**	**35**	**204**	

girls (145 cases, 60.7%). A total of 105 cases (30%) had Marsh 0, 1 that excluded from the study. Children with elevated TTG antibodies, but with Marsh 0 or 1 changes on histology were regarded as potential celiac and followed at intervals on an individual basis depending on their symptoms. The 35/239 cases with negative TTG (Mean ± SD: 4.9 ± 3.7) but strong clinical suspicion for CD, all had Marsh 2, 3 changes on histopathology. Description of subjects based on Marsh score and clinical groups is shown in Table 4.

Discussion

Although the CD is believed to be relatively common in Iran little data are available regarding the patterns of presentation in the children from this region. This retrospective study provides a picture of children with a high suspicion for the CD in the South- East of Iran. Our study showed that CD has similar clinical presentations among Iranian children as found in other parts of the world. Common clinical manifestations at initial presentation include abdominal pain, distension and chronic diarrhea as the most frequent GI symptoms and under nutrition, decreased bone age and anemia as the most common extra intestinal manifestations.

The mean age at diagnosis was 6.8 ± 3.9 years with 82% occurrence in subjects > 2 years old. This finding is in contrast with the study by Baudon, et al. that reported the occurrence of the first signs of CD before one year of age in 73%.[14] Recent publications have shown the mean age of newly diagnosed patients has increased over the past few years.[15] Delays in diagnosis of CD in our study could in part be attributed to misdiagnosis of common parasitic infestations in the region, lack of CD awareness by pediatricians and living in rural and urban areas with limited resources capable of checking TTG status.

Reports from India have shown more GI symptoms with diarrhea, FTT, distension and less often abdominal pain, vomiting and constipation.[18,19] In addition, a study of Iranian adults with celiac disease showed diarrhea and bloating as the classic presentations of CD.[20] One other study identified a high prevalence of CD antibodies among patients with GI symptoms.[21] While the majority of patients in our study had GI symptoms, these were seldom suggestive of a typical malabsorption pattern. Forty one of our patients experienced recurrent abdominal pain as one of their chief complaints. Testing for CD in children with RAP may not be considered unless additional alarm symptoms are present.[22] A previous study from Iran involving 301 children with RAP, estimated the prevalence of CD to be 1.3% in this group.[23] These findings, together with the frequency of abdominal pain as a presenting feature in our study, suggest physicians to consider earlier testing for CD in children with RAP.

A high rate of growth failure was a noticeable finding in our study. Growth failure could be attributed to nutrient malabsorption, reduced intake and poorer socioeconomic situation especially in this region. Although FTT is still a typical manifestation of CD in the pediatric age group, severe growth delay is now much less commonly observed in developed countries.[16] In addition, recent publications demonstrated a change in the pattern of CD with an increasing percentage of overweight children.[24,25] In contrast, in our study it was unusual to find overweight children with CD (1 case). Therefore, diagnosis of CD should be considered in overweight children.

Besides growth failure, decreased bone age and anemia were among the most common extra- intestinal manifestations. Anemia is a well-known presenting manifestation of CD and iron deficiency anemia refractory to treatment may be the sole manifestation of CD in 8.6% – 19% of children.[26–28] Some studies report a higher frequency of iron deficiency and intestinal complaints and less FTT in children with CD than those without CD.[16] Another significant finding in our study was low bone mass (35%). Therefore, identifying and treating children with CD is critical for preventing long-term consequences of decreased bone density. Markedly reduced bone mineral density has been observed in children with untreated CD, even in asymptomatic cases.[29,30] Studies have shown strict avoidance of gluten causes improvement of bone mineralization, within a year. [31]

Our study showed that the classic presentation of CD with a predominance in females is still a relatively a common feature (30%) in Iran. Similarly, another study from Iran showed CD is more frequent in children with diarrhea than previously suspected.[32] Studies from Europe and North America have shown a decrease in the relative percentage of classical forms to 15% in recent years.[33] In contrast, a recent study in Spain has shown the most frequent clinical presentation of CD to be of the classical symptom in 71%.[34] While most cases of classical CD are still diagnosed before the end of the second year of life,[35] the proportion is declining.[16,27]

Recent publications describe a changing face of childhood CD with an increase in non-classical and silent forms occurring in older children.[8,9,36] In addition, the proportion of children with CD and GI manifestations has decreased while patients with non-GI manifestations and asymptomatic patients were identified via targeted screening have increased.[36,37] These findings of the current study are not consistent with other studies that suggest GI manifestation is relatively less common as an initial presentation of CD;[36,37] however, our findings support the previous research from Saudi Arabia where GI manifestations were still most common.

Serological tests using the TTG-IgA antibody is a valuable marker for diagnosis of CD as demonstrated by the 239 definite cases of CD. However, 35/239 cases had negative TTG with positive histologic changes. This emphasizes that serological tests are not 100% accurate and if the clinical suspicion for CD is strong the child should undergo an intestinal biopsy even if the serological test is negative. Lack of ability to perform deamidated gliadin peptide antibodies (DGP-IgA or IgG) or HLA typing in this study, especially in children below 2 years old, could possibly account for some of the negative tests in the study.

The majority of our cases had a definite CD with preference in girls (61%). The severity of the mucosal lesion showed no significant differences with age. Duodenal biopsy is the gold standard for the diagnosis of CD, but it may be avoidable based on revised ESPGHAN guidelines in patients with typical CD and increased levels of TTG-IgA (>10 times above the upper limit) combined with positive HLA-DQ2 and/or DQ8 heterodimers.[1] As we did not have access to these additional tests, a non-biopsy diagnosis is not yet an option for the children in Iran. Success with this approach may be dependent on the pretest probability of CD and appropriate use of cutoffs.[39] The severity of the villous atrophy in the children of this study may indicate a long delay in diagnosis in some of these cases.

Associations between CD and other autoimmune diseases, as

well as higher frequency in first-degree family member are well described.[40,41] In this study, 22 patients were identified via the screening of first-degree relatives. Screening of at-risk groups (e.g. first-degree relatives, type 1 diabetes mellitus (T1DM), Down syndrome, and autoimmune thyroid disease) is recommended by recent ESPGHAN guidelines. [1] In our study, hypothyroidism and T1DM was the most frequent associated condition in the children with CD which is consistent with other studies.[35,42] Therefore, screening at-risk individuals with serological tests could increase the positive predictive value of serological tests and identify at risk subjects.[43]

There are some limitations to our study. Living far from the facility resources in our hospital could be a reason that many children with milder forms of presentation remain undiagnosed. In the same way, many children with chronic diarrhea may be presumed to have intestinal infections, which are common in Iran and hence will not be referred for testing. Other limitations in the study were the unavailability of other tests such as DGP-IgA or IgG or HLA typing and the retrospective nature of the study. Finally, as not all cases were reviewed by a single pathologist who is knowledgeable about CD, it is possible in some cases the diagnosis was missed. Despite these limitations, findings in this study serve as an important reminder to physicians living in the larger region to consider the diagnosis of CD more frequently and be prepared to perform the appropriate screening tests.

Acknowledgments

We thank all participants of this study.

References

1. Husby S, Koletzko S, Korponay–Szabo IR, Mearin ML, Phillips A, Shamir R, et al. European Society for Pediatric Gastroenterology, Hepatology, and Nutrition guidelines for the diagnosis of coeliac disease. J *Pediatr Gastroenterol Nutr*. 2012; 54(1): 136 – 160.
2. Hill ID, Dirks MH, Liptak GS, Colletti RB, Fasano A, Guandalini S, et al. Guideline for the diagnosis and treatment of celiac disease in children: Recommendations of the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition. *J Pediatr Gastroenterol Nutr*. 2005; 40(1): 1 – 9.
3. Nejad MR, Rostami K, Emami MH, Zali MR, Malekzadeh R. Epidemiology of celiac disease in Iran: A review. *Middle East J Dig Dis.* 2011; 3(1): 5 – 12.
4. Dehghani SM, Haghighat M, Mobayen A, Rezaianzadeh A, Geramizadeh B. Prevalence of celiac disease in healthy Iranian school children. *Ann. Saudi Med.* 2013; 33(2): 159.
5. Farahmand F, Mir–Nasseri MM, Shahraki T, Yourdkhani F, Ghotb S, Modaresi V, et al. Prevalence of occult Celiac Disease in healthy Iranian school age children. *Arch Iran Med*. 2012; 15(6): 342.
6. Mustalahti K, Catassi C, Reunanen A, Fabiani E, Heier M, McMillan S, et al. The prevalence of celiac disease in Europe: Results of a centralized, international mass screening project. *Ann Med.* 2010; 42(8): 587 – 595.
7. Fasano A, Catassi C. Coeliac disease in children. *Best Pract Res Clin Gastroenterol.* 2005; 19(3): 467 – 478.
8. Roma E, Panayiotou J, Karantana H, Constantinidou C, Siakavellas SI, Krini M, et al. Changing pattern in the clinical presentation of pediatric celiac disease: A 30–year study. *Digest.* 2009; 80(3): 185 – 191.
9. Savilahti E, Kolho KL, Westerholm-Ormio M, Verkasalo M. Clinics of coeliac disease in children in the 2000s. *Acta Paediatr*. 2010; 99(7): 1026 – 1030.
10. Marsh M, Johnson M, Rostami K. Mucosal histopathology in celiac disease: A rebuttal of Oberhuber's sub–division of Marsh III. *Gastroenterol Hepatol Bed Bench.* 2015; 8(2): 99 – 109.
11. Walker–Smith JA, Guandalini S, Schmitz J, Shmerling DH, Visakorpi JK. Revised criteria for diagnosis of celiac disease. Report of Working Group of European Society of Paediatric Gastroenterology and Nutrition. *Arch Dis Child*. 1990; 65: 909 – 911
12. De Onis M, Blössner M. The World Health Organization global database on child growth and malnutrition: Methodology and applications. *Int. J. Epidemiol.* 2003; 32(4): 518 – 526.
13. Robins EB, Blum S. Hematologic reference values for African American children and adolescents. *Am J Hematol*. 2007; 82(7): 611 – 614.
14. Baudon JJ, Dabadie A, Cardona J, Digeon B, Ginies JL, Larchet M, et al. Incidence of symptomatic celiac disease in French children. *Presse Medicale*. 2001; 30(3): 107 – 110.
15. Tapsas D, Hollén E, Stenhammar L, Fälth–Magnusson K. The clinical presentation of coeliac disease in 1030 Swedish children: Changing features over the past four decades. *Dig Liver Dis*. 2016; 48(1): 16 – 22.
16. Lurz E, Scheidegger U, Spalinger J, Schöni M, Schibli S. Clinical presentation of celiac disease and the diagnostic accuracy of serologic markers in children. *Eur. J. Pediatr.* 2009; 168(7): 839 – 845.
17. Ivarsson A, Persson LÅ, Nyström L, Hernell O. The Swedish coeliac disease epidemic with a prevailing twofold higher risk in girls compared to boys may reflect gender specific risk factors. *Eur J Epidemi*. 2003; 18(7): 677 – 684.
18. Poddar U, Thapa BR, Singh K. Clinical features of celiac disease in Indian children: are they different from the West? *J Pediatr Gastroenterol Nutr*. 2006; 43(3): 313 – 317.
19. Rawal P, Thapa B, Nain C, Prasad K, Singh K. Changing spectrum of celiac disease in India. *Iran J Pediatr*. 2010; 20(4): 459 – 465.
20. Ehsani–Ardakani MJ, Rostami Nejad M, Villanacci V, Volta U, Manenti S, Caio G, et al. Gastrointestinal and non–gastrointestinal
21. presentation in patients with celiac disease. *Arch Iran Med*. 2013; 16(2): 78 – 82.
22. Rostami Nejad M, Rostami K, Pourhoseingholi MA, Nazemalhosseini Mojarad E, Habibi M, Dabiri H, et al. Aypical presentation is dominant and typical for coeliac disease. *J Gastrointestin Liver Dis*. 2009; 18(3): 285 – 291.
23. American Academy of Pediatrics. Subcommittee on Chronic Abdominal Pain. Chronic abdominal pain in children. *Pediatrics.* 2005; 115: 812 – 815.
24. Farahmand F, Modaresi V, Najafi M, Khodadad A, Moetamed F, Modarres Z. Prevalence of celiac disease in Iranian children with recurrent abdominal pain referred to a pediatric referral center. *Iran J Pediatr*. 2011; 21(1): 33 – 38.
25. Telega G, Bennet TR, Werlin S. Emerging new clinical patterns in the presentation of celiac disease. *Arch Pediatr Adolesc.* 2008; 162(2): 164 – 168.
26. Venkatasubramani N, Telega G, Werlin SL. Obesity in pediatric celiac disease. *J Pediatr Gastroenterol Nutr.* 2010; 51: 295 – 297.
27. Garampazzi A, Rapa A, Mura S, Capelli A, Valori A, Boldorini R, et al. Clinical pattern of celiac disease is still changing. *J Pediatr Gastroenterol Nutr*. 2007; 45: 611 – 614.
28. Balamtekin N, Uslu N, Baysoy G, Usta Y, Demir H, Saltik-Temizel IN, et al. The presentation of celiac disease in 220 Turkish children. *Turk. J. Pediatr.* 2010; 52: 239 – 244.
29. Economou M, Karyda S, Gombakis N, Tsatra J, Athanassiou-Metaxa M, et al. Subclinical celiac disease in children: Refractory iron deficiency as the sole presentation. *J. Pediatr. Hematol. Oncol.* 2004; 26: 153 – 154.
30. Kalayci AG, Kansu A, Girgin N, Kucuk O, Aras G. Bone mineral density and importance of a gluten–free diet in patients with celiac disease in childhood. *Pediatrics.* 2001; 108(5): e89
31. Mustalahti K, Collin P, Sievänen H, Salmi J, Mäki M. Osteopenia in patients with clinically silent coeliac disease warrants screening. *The Lancet*. 1999; 354(9180): 744 – 745.
32. Kavak US, Yüce A, Koçak N, Demir H, Saltik IN, Gürakan F, et al. Bone mineral density in children with untreated and treated celiac disease. J *Pediatr Gastroenterol Nutr*. 2003; 37(4): 434 – 436.
33. Imanzadeh F, Sayyari AA, Yaghoobi M, Akbari MR, Shafagh H, Farsar AR. Celiac disease in children with diarrhea is more frequent than previously suspected. *J Pediatr Gastroenterol Nutr.* 2005; 40(3): 309 – 311.
34. McGowan KE, Castiglione DA, Butzner JD. The changing face of childhood celiac disease in North America: impact of serological testing. *Pediatrics.* 2009; 124: 1572 – 1578.
35. Cilleruelo ML, Roman–Riechmann E, Sanchez–Valverde F, Donat E, Manuel–Ramos J, Martín–Orte E, et al. Spanish national registry of celiac disease: Incidence and clinical presentation. J *Pediatr*

Gastroenterol Nutr. 2014; 59(4): 522 – 526.
36. Iwańczak B, Matusiewicz K, Iwańczak F. Clinical picture of classical, atypical and silent celiac disease in children and adolescents. *Adv Clin Exp Med*. 2013; 22 (5): 667 – 673.
37. Garnier-Lengliné H, Brousse N, Candon S, Goulet O, Ruemmele FM, Schmitz J. et al. Have serological tests changed the face of childhood coeliac disease? Aretrospective cohort study. *BMJ Open*. 2012; 2(6): e001385
38. Ravikumara M, Tuthill DP, Jenkins HR. The changing presentation of coeliac disease. *Arch. Dis. Child*. 2006; 91: 969 – 971.
39. Sarkhy AA, El Mouzan MI, Saeed E, Alanazi A, Alghamdi S, Anil S, et al. Clinical Characteristics of Celiac Disease and Dietary Adherence to Gluten–Free Diet among Saudi Children. J *Pediatr Gastroenterol Nutr*. 2015; 18(1): 23 – 29.
40. Mills JR, Murray JA. Contemporary celiac disease diagnosis: Is a biopsy avoidable? *Curr Opin Gastroenterol*. 2016; 32(2): 80 – 85.
41. Denham JM, Hill ID. Celiac disease and autoimmunity: review and controversies. Curr *Allergy Asthma*. 2013; 13(4): 347 – 353.
42. Rubio-Tapia A, Van Dyke CT, Lahr BD, Zinsmeister AR, El-Youssef M, Moore SB, et al. Predictors of family risk for celiac disease: A population–based study. *Clin Gastroenterol Hepatol*. 2008; 6: 983 – 987.
43. Kuloglu Z, Kirsachoglu CT, Kansu A, Eusari A, Girgin N. Celiac disease: Presentation of 109 children. *Yonsei Med J*. 2009; 50: 617 – 623.
44. Valitutti F, Barbato M, Cucchiara S. Screening celiac disease in at-risk groups: Effect of diagnosis on perceived health of children and their families. *J Pediatr Gastroenterol Nutr*. 2012; 55(4): 365.