Celiac disease in Saudi children

Evaluation of clinical features and diagnosis

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ABSTRACT

الأهداف: وصف العوارض السريرية والتشخيص بما في ذلك الاختبارات المصلية والنتائج النسيجية في الأطفال الذين يعانون من مرض السيلياك (الداء الزلاقي).

الطريقة: أُجريت هذه الدراسة بأثر رجعي على جميع الأطفال (أقل من 18 عاماً) المصابين بمرض السيلياك لمدة 6 سنوات في مركز الرعاية الصحية الثلاثية الخاص في مدينة الرياض في المملكة العربية السعودية وشملت المعلومات التي تم جمعها الديموغرافيات والعوارض السريرية وطرق التشخيص لعلم الامصال والامعاء الدقيقة حسب تصنيف مارش.

النتائج: تم تأكيد اصابة 59 طفل بمرض السيلياك، ثلاثون منهم ذكور بنسبة بلغت (50.8%) وكان متوسط العمر 8 سنوات (تتراوح من 1 إلى 16 عام) كان متوسط مدة الأعراض قبل التشخيص 2.3 (±1.5). كان المرض موجود بصورته التقليدية بنسبة 30.5% في حين أن 69.5% كانت لديهم عوارض غير تقليدية أو تنتمي لمجموعات عالية الخطورة لمرضى السيلياك مثل اولئك الذين يعانون من سكري النوع الأول والتهاب الغدة الدرقية الناجم عن المناعة الذاتية والمصابين بمتلازمة داون أو اشقائهم المصابين بها. أكثر الاعراض شيوعاً كانت فشل النمو يليها قصر القامة ثم الألم في البطن واخيراً الاسهال المزمن. كانت الاجسام المضادة للجسم المضاد للالترانس غلوتاميناز النسيجي ايجابية بنسبة 91.5%. لم يختلف عيار الاجسام المضادة بين ممن يعانون من المرض بصورته التقليدية وغير التقليدية وكانت جميع نتائج الخزعة حسب تصنيف مارش تتوافق مع مرض السيلياك.

الخاتمة: عادة مايكون لدى الأطفال المصابين بمرض السيلياك خصاذص غير تقليدية. ينبغي وبشده مراعاة الاشتباه بهذا المرض عند اجراء الفحوصات الطبية في المرضى الأطفال. وينبغي فحص المجموعات ذات المخاطر العالية في وقت مبكر لتجنب المضاعفات المرتبطة مرض السيلياك غير المعالج.

Objectives: To characterize the clinical presentations and diagnosis including serological tests and histopathological findings in children with celiac disease.

Methods: All children (<18 years) with confirmed celiac disease diagnosed over a 6 year period at a private tertiary care health care center in Riyadh, Saudi Arabia were studied retrospectively. Information collected included demographics, clinical presentation and diagnostic modalities with serology and small intestinal histology reported by Marsh grading.

Results: A total of 59 children had confirmed celiac disease. Thirty (50.8%) were male. Median age was 8 years (range 1 to 16 years). The mean duration of symptoms before diagnosis was 2.3 (±1.5) years. Classical disease was present only in 30.5%, whereas 69.5% had either non-classical presentations or belonged to high risk groups for celiac disease such as those with type-1 diabetes, autoimmune thyroiditis, Down syndrome and siblings. Failure to thrive was the most common presentation followed by short stature, abdominal pain and chronic diarrhea. Anti-tissue transglutaminase antibody was positive in 91.5%, and titers were no different between those with classical and non-classical disease. All had Marsh-graded biopsy findings consistent with celiac disease.

Conclusion: Children with celiac disease usually present with non-classical features. A high index of suspicion needs to be maintained to consider this disorder in the diagnostic workup of pediatric patients. High risk group should be screened early to avoid complications associated with untreated celiac disease.

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Celiac disease (CD) is a chronic autoimmune disorder in which ingestion of gluten (a group of proteins in wheat, rye, and barley) leads to villous atrophy in genetically susceptible individuals. Prevalence of CD is approximately 0.5 to 1% in general population.[1] The true prevalence of CD in Kingdom of Saudi Arabia (KSA) is not known due to lack of a national epidemiological study, but regional data shows that it is a common disorder in this part of the world.[2,3,4] Celiac disease has a broad clinical spectrum with 4 patterns recognized as per Oslo definition.[5] In classical (typical) CD, the patient presents with features of malabsorption such as diarrhea, steatorrhea, and weight loss or growth failure. In non-classical (atypical) CD, signs and symptoms of malabsorption are absent or minimal with patients having other intestinal or extra-intestinal symptoms. This is becoming a predominant mode of presentation especially in older children and adolescents. Some symptoms may overlap between these 2 types. In both classical and non-classical CD, the serologic test results are abnormal and varying degrees of villous atrophy is present. In subclinical CD, previously referred to as asymptomatic CD, the disease is below the threshold of clinical detection without symptoms or signs sufficient to trigger CD testing in routine clinical practice. Some of these individuals might be screened as they have a high risk of developing CD. These patients will have abnormal serologic test results, as well as villous atrophy. In potential CD, previously called latent CD, the patient has an abnormal antibody test, but normal small intestinal histology. Several of these individuals will develop the intestinal lesion over time, thus requiring careful monitoring and follow-up. Physicians need to be aware that CD is a common disorder, has diverse clinical presentations and a timely diagnosis is essential to avoid serious complications of untreated disease.[6,7] With the availability of highly sensitive and specific serological markers such as anti-tissue transglutaminase antibody (tTGA) and anti-endomysial antibody (EMA), CD is being found in minimally symptomatic individuals or in those at high risk of having the disorder such as individuals with type-1 diabetes mellitus, autoimmune thyroiditis (and other autoimmune disorders) and first/second-degree relatives.[1] Small intestinal biopsy is the confirmatory test for the diagnosis of CD and its treatment involves a strict gluten-free diet for life.

The aim of the study was to characterize the clinical presentation and diagnosis including serological tests and histopathological findings using Marsh grading in children with CD.

Methods. All children with a diagnosis of CD from January 2009 to January 2015 at a private tertiary care hospital, Suleman Al-Habib Medical Group, Riyadh, KSA were studied retrospectively. The data was collected from electronic records of patients using search terms: celiac disease, gluten sensitive enteropathy, chronic diarrhea, malabsorption, and small intestinal biopsies. Only children under the age of 18 years were included. Information recorded for analysis included age, gender, nationality, clinical presentation, available biochemical parameters including serological markers and small intestinal biopsy interpretation using Marsh grading system.[8] All patients had confirmed CD based on serological markers including IgA-tTGA and/or IgG-tTGA and/or changes on histology of the small intestinal mucosal biopsies. Cases with negative serology but positive histology further probed for the reasons why small intestinal biopsies were performed. Genetic studies for HLA-DQ2/DQ8 had not been performed in any patients primarily due to the cost reasons in a private clinic setup. Categorical data were summarized as numbers and percentages, whereas continuous data were summarized as mean and standard deviation. Comparison between groups for categorical variable was carried out using chi-square test or Fisher's exact test, whereas for continuous data student t-test or Mann Whitney u test were used. Any association with p-value<0.05 was considered statistical significant. All statistical analyses were performed using SAS version 9.2 (SAS Institute, Inc, Cary, NC). The study was approved by the Institutional Ethics Review Board and conducted according to the principles of the Helsinki Declaration.

Results. Of the 318 small intestinal biopsies performed on children for various reasons over a period of 6 years, 64 (20.1%) had received a diagnosis of CD. Data was missing in 5 patients, so 59 cases were included in the study. The demographic and general characteristics of patients are shown in **Table 1**. Thirty (50.8%) were male, median age at time of presentation was 8 years (range 1 to 16 years). The mean duration of symptoms before the diagnosis was 2.3±1.5 years with almost 95% being of Saudi origin. Classical symptoms

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were present in 18 (30.5%), while 41 (69.5%) had non-classical (atypical) presentation. The comparison of various clinical features in the classical and non-classical (atypical) of all patients is shown in **Table 2**. Diarrhea is a hallmark of malabsorption and this symptom was primarily used to designate classical CD. Failure to thrive was most common symptom in classical CD. Many also had abdominal distention and abdominal pain. Short stature was most common presentation of non-classical CD. A significant proportion of children had growth retardation, in both classical and non-classical CD groups. Clinical pattern of high risk patients with CD (n=19) including those with type-I diabetes, Down syndrome, autoimmune thyroiditis and siblings is shown in **Table 3**. These patients were mainly picked up on screening. However, 4 had classical symptoms. Of these, 3 had type-1 diabetes and 1 had Down syndrome. **Table 4** lists the laboratory and histological findings of the patients. The IgA-tTGA was positive in 54 (91.5%) and IgG-tTGA positive in 48 (81.3%). Both tests were performed on all the patients. However, data on total serum IgA was available only in 3 patients. There was no difference in the mean IgA-tTGA and/or IgG-tTGA titers between the 2 groups. Most (n=52) had Marsh grade 3 lesion on histology of small intestinal mucosa.

Discussion. Celiac disease is a common disorder in children. Studies from Arab countries has shown a rising trend,[2-4,9] but there are limited data on the clinical presentation and diagnostic evaluation of CD in Saudi children. Celiac disease has traditionally been considered a disorder of late infancy and early

Table 1 - The frequency distribution of the causes of burns in patients demographic characteristics of patients with celiac disease (n=59)

Variables	Classical	Non-classical	*P*-value
Age at presentation (years)(mean ±SD)	6.4 ± 3.4	9.0 ± 4.0	0.022
Duration of symptoms (years) (mean ±SD)	2.4 ± 1.5	2.15 ±1.5	0.523
Male n (%)	8 (44.4)	22 (53.6)	0.514
Female n (%)	10 (55.5)	19 (46.3)	
Saudi origin/non-Saudi n (%)	17/18 (94.4)	39/41 (95.1)	

Table 2 - Clinical pattern of patients with celiac disease (n=59).

Clinical Features	Classical presentation n (%)	Non-classical presentation n (%)	*p*-value
Chronic diarrhea	18	0	
Recurrent abdominal pain	6 (33.3)	10 (24.4)	0.47
Abdominal distension	5 (27.8)	4 (9.8)	0.076
Failure to thrive	13 (72.2)	6 (14.6)	<0.001
Vomiting	2 (11.1)	0	0.03
Short stature	2 (11.1)	12 (29.3)	0.13
Pallor	0	5 (12.2)	0.12
Clubbing	6 (33.3)	4 (9.7)	0.026
Z score (weight for age) (mean±SD)	17/18 -1.82±1.90	38/41 -1.6±1.4	0.034
Z score (height for age) (mean±SD)	17/18 -2.17±1.4	38/41 -2.15±1.14	0.025

Table 3 - Clinical pattern of high risk patients with celiac disease (n=19).

High risk group	Classical presentation n (%)	Non-classical presentation n (%)	*P*-value
Type-1 diabetes	3 (16.7)	10 (24.4)	0.51
Down syndrome	1 (5.6)	2 (4.9)	0.91
Hypothyroidism	0	2 (4.9)	0.34
Sibling screening	0	1 (2.4)	0.54

Table 4 - Biochemical, serological, and histological results using Marsh classification in patients with celiac disease (n=59).

Laboratory Investigations	Classical presentation	Non-classical presentation	*P*-value
Hemoglobin (mean ±SD) g/L	10.8±1.1	11.2±1.7	0.537
Serum iron (mean ±SD) µmol/L	12.4±5.2	17.1±6.8	0.023
Serum calcium (mean ±SD) mmol/L	2.1±0.8	1.99±0.8	0.063
Alkaline phosphatase (mean ±SD) IU/L	208±73	234±130	0.790
IgA-tissue transglutaminase antibody (mean ±SD) U/mL	191.5±113.4	179.6±117.4	0.718
IgG-tissue transglutaminase antibody (mean ±SD) U/mL	116.6 ±94.1	122.1 ±72.2	0.809
Marsh grading (n)			
Type 1	2	1	
Type 2	1	3	
Type 3	15	37	
Type 3a	-	1	
Type 3b	1	2	
Type 3c	14	34	

Marsh grading - Marsh 0 - normal, Marsh 1 - >30 intraepithelial lymphocytes (IELs) per 100 enterocytes (infiltrative), Marsh 2 - >30 IELs per 100 enterocytes, crypt hyperplasia (hyperplastic), Marsh 3 - >30 IELs per 100 enterocytes, crypt hyperplasia, villous atrophy (destructive),(type 3a = partial villous atrophy, type 3b = subtotal villous atrophy, type 3c = total villous atrophy)

childhood. However, as our study demonstrates, it is not limited to that age group. Classical CD is usually seen in infants and toddlers whereas non-classical type is more common in older children.[10] In our study, the mean age of presentation was 6.4 ±3.4 years for classical CD and 9±4.0 years for non-classical CD. Classical CD used to present at an earlier age with malabsorptive symptoms such as chronic diarrhea, abdominal distension and failure to thrive.[11] On the other hand, non-classical cases are detected during screening for other presentations such as isolated short stature, vomiting, constipation, recurrent abdominal pain and iron deficiency anemia. Malabsorptive picture with diarrhea is seen in classical CD. Along with wasting and distended abdomen, these patients may have digital clubbing. In our study, clubbing was present in a third of cases of classical CD, significantly more frequent than in those with non-classical CD. Children with classical CD also had significantly lower z scores for both weight and height, compared with those with non-classical CD. Individuals that are at high risk for developing CD include those with type-1 diabetes, autoimmune thyroiditis and Down syndrome.[1,12,13]

In our study, more than 2-third (69.5%) of cases of CD had either non-classical presentation such as isolated short stature or were in a high-risk group. It is worth noting that short stature or failure to thrive can manifest in the absence of overt diarrhea. Hematological and biochemical derangements are often seen in cases with CD, usually in those with malabsorptive presentation. Isolated iron deficiency anemia and rickets (from calcium/vitamin D deficiency) have also been reported.[14] Our study showed microcytic hypochromic anemia in both the groups but significantly lower level of serum iron in the classical CD group (p=0.023). Availability of serological assays has made it possible to detect CD in the subclinical group.[15,16]

In our study, patients were screened with IgA- tTGA (91.5% were positive) and IgG-tTGA (81.3% were positive) and this data is consistent with other reports.[16] Sero-negative CD occurs but is uncommon. Selective IgA deficiency is common in CD and total IgA should be measured when employing an IgA-based serological test. In IgA deficiency, one has to rely on an IgG-based test. Small intestinal biopsy is the confirmatory test for CD. The biopsies are taken endoscopically from the bulb and distal duodenum and reported using the Marsh grading as summarized in **Table 4.**[8,17]

Most of patients in our study had Marsh grade 3 lesion, the most common being 3c (total villous atrophy). Villous atrophy is a hallmark of CD. However, there were 3 patients with Marsh 1 lesion (no villous atrophy or crypt hyperplasia) and one could question the diagnosis of CD in these cases. However, they all had elevated IgA-tTGA titers and also had symptoms, with 2 having diarrhea/malabsorption and one chronic abdominal pain. The small intestinal lesion in CD has a spectrum of severity. It can also be patchy and can potentially be missed on biopsies. Therefore, in a symptomatic patient with a positive serological test, the diagnosis of CD

can be entertained with some caution even with Marsh 1 lesion. For the 4 patients in the study with Marsh grade 2 lesions, all were symptomatic and had elevated IgA-tTGA titers. It is also important to note that if the patients reduce or remove gluten from the diet by the time they come for biopsy, the small intestinal histology can improve significantly. However, the retrospective nature of the study precludes determining if this was the case in these patients with Marsh 1 and 2 lesions. It is for this reason that the primary care physician should always instruct the families not to remove gluten from the diet of the child before endoscopic small intestinal biopsies are completed.

Study limitations. Given the retrospective design, complete data extraction of participants is not always possible. Also, this is a single center study from a tertiary care health care institution and caution needs to be exercised in generalizing the results.

In conclusion, children with celiac disease in Saudi Arabia present with both classical and non-classical forms, the latter being more common and sometimes without intestinal symptoms. Patients with classical CD tend to be younger, have poor growth, have digital clubbing and iron deficiency. Patients with non-classical CD may have no diarrhea, so physicians need to maintain a high index of suspicion for this disorder while assessing these children. Early screening with tTGA should be considered in such cases and diagnosis confirmed with small intestinal biopsies using Marsh grading. A large, prospective, population-based study is needed to more comprehensively assess the clinical patterns of CD in Saudi children.

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