Value of clinical data in diagnosis of symptomatic celiac disease in children

Nashwan M. Al-Hafidh
Department of Medicine, Pediatric Division, Nineveh College of Medicine, University of Mosul.

(Ann. Coll. Med. Mosul 2012; 38 (1): 46-53).
Received: 12th Sep. 2011; Accepted: 4th Dec. 2011.

ABSTRACT

Objective: To identify the value of clinical data in diagnosis of celiac disease (CD) in children.
Patients and methods: a prospective study was conducted in Mosul city during the period from 30th of October 2007 to 30th of April 2011. A total of 57 patients (39 males, 18 females) aged more than 6 months on gluten containing diet presented with symptoms suggestive of (CD) were evaluated clinically and serologically using IgA human recombinant tissue transglutaminase antibody. (IgA anti tTG2). Multiple duodenal biopsies were performed for every patient enrolled in this study. CD cases had been followed up 6 months after a gluten free diet (GFD) by weight measurement and the mentioned serological testing.
Results: A total of 29 (50.9%) out of 57 symptomatic patients with mean age of 56.1 months, demonstrated positive biopsy results for celiac disease. Failure to thrive (FTT) was noticeable in 25 (86.2%) of studied patients with celiac disease followed by anemia, abdominal distension, offensive stool and chronic diarrhea in decreasing frequency. Catch up of weight was not achieved in 10 (43.5%) out of 23 CD patients with FTT whose (IgA anti tTG2) normalized after 6 months of GFD.
Conclusions: The diagnosis of celiac disease on the basis of clinical features alone was incorrect in (49.1%) cases, indicating that diagnosis and lifelong GFD treatment is not justifiable relying on clinical data. Catch up of weight cannot be relied upon as an early marker of clinical improvement in patients with proven adherence to GFD.
The result of this study emphasizes the importance of increasing awareness of the accurate tools in diagnosis of CD in children based on serological and biopsy evidences.

Keywords: Celiac disease, clinical diagnosis, catch up of weight.

الخلاصة

هدف الدراسة: معرفة قيمة البيانات السريرية في تشخيص الجواف لدى الأطفال.
طريقة البحث والمشاركون: هذه دراسة مستقبلية أجريت في عيادة خاصة في مدينة الموصل، خلال الفترة من ٣٠ تشرين الأول عام ٢٠٠٧ ولغاية ٣٠ نيسان عام ٢٠١١. ضمت العينة المدروسة (٥٧) مريضا (٣٩ ذكرا، ١٨ أنثى) تجاوزت أعمارهم الستة أشهر. الكل كان يتناول قبل الدراسة طعاما يحتوي على الغروين ولديهم أعراضا موحية بالجواف. تم تقييم كل أفراد العينة سريريا وبالفحص المصلي لفحص الأجسام المضادة من نوع IgA human recombinant anti tTG2 وأخذت خزعات من مناطق متعددة من الإثني عشري لكل أفراد العينة. تمت متابعة حالات الجواف بعد ستة أشهر من تناول الطعام الخالي من الغروين بقياس الوزن والفحص المصلي المذكور.
النتائج: كانت نتيجة فحص الخزعة لمرض الجواف موجبة لدى (٢٩) مريضا والذين شكلوا نسبة ٥٠,٩% من العدد الكلي للمرضى والذي بلغ معدل أعمارهم (٥٦,١) شهرا، وقد لوحظ فشل في النمو في ٢٥ (٨٦,٢%) مريض تبعه فقر الدم، انتفاخ البطن، غائط كريه الرائحة وإسهال مزمن بتردد متناقص. لم يتحقق اللحاق بالوزن في ١٠ (٤٣,٥%) من أصل ٢٣

مريضاً بالجواف مع فشل النموعلى الرغم من رجوع مستوى فحصهم المصلي الى الطبيعي بعد ٦ أشهر من تناول الطعام الخالي من الغروين.
الاستنتاجات: لا مبرر لتشخيص الجواف والعلاج بالطعام الخالي من الغروين المعتمد على البيانات السريرية لان تشخيص مرض الجواف المستند على االمظاهر السريرية لوحدها كان خاطئا في ٤٩,١% من الحالات. لايمكن الاعتماد على متابعة الوزن كعلامة مبكرة للتحسن السريري في المرضى الذين لديهم التزام مثبت مصليا بالطعام الخالي من الغروين.
تؤكد نتائج هذه الدراسة على أهمية زيادة التوعية بالوسائل الدقيقة المبنية على أدلة نسيجية ومصلية لتشخيص مرض الجواف لدى الأطفال.

Celiac disease (CD) is an immune - mediated enteropathy caused by permanent sensitivity to gluten in genetically susceptible individuals [1]. It occurs in genetically predisposed individuals [2] and marked geographical variations do appear to exist [3].

The prevalence of celiac disease in Tunisian schoolchildren, estimated to be about 1/157 which is close to the European prevalence [2]. In Jordan the serological prevalence was estimated to be 1:124 in schoolchildren [4], whereas the average annual incidence in Kuwait is 1:3000[5]. To date no prevalence of celiac disease data were reported from Iraq.

Symptoms can begin at any age when gluten-containing foods are given; typical symptoms include diarrhea, offensive stools, abdominal distention, decreased appetite, failure to thrive, and iron-deficiency anemia not responding to oral iron therapy, edema and short stature [1,6,7]. It is recommended that CD be an early consideration in the differential diagnosis of children with FTT and persistent diarrhea. Limited data suggest the prevalence of CD may be increased 2–10 times in children with some of these GI symptoms or occur in up to 5% of cases [8].

Definitive diagnosis of celiac disease requires small intestinal biopsy [1]. According to the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN), there is a recognized spectrum of histologic features varying from mild to severe as described by Marsh et al[8]. Marsh classified the histologic changes of CD as Type 0 or preinfiltrative stage (normal), Type 1 or infiltrative lesion (increased intraepithelial lymphocytes), Type 2 or hyperplastic lesion (Type 1+ hyperplastic crypts), Type3 or destructive lesion (Type 2 + variable degree of villous atrophy) and Type 4 or hypoplastic lesion (total villous atrophy with crypt hypoplasia) [8]. None of the individual features is pathognomonic for CD, as each may be seen in other disease states however, the combination of histopathologic features in a compatible clinical setting is sufficient evidence for a diagnosis of CD and there is good evidence that villous atrophy (Marsh Type 3) is clearly a feature of CD [8, 9]. Despite the increasing importance of serological methods, the diagnosis of CD is still based on histological criteria [8-10] followed by a therapeutic response to a gluten free diet [9]. The mucosal involvement can be patchy, so multiple biopsies must be obtained [1].

Given the lifelong nature of the disease, the attendant need for an expensive socially inconvenient gluten free diet (GFD) and the sporadic local practice of a trail of GFD without confirmations of CD diagnosis in spite of availability of CD serological screening tests leads the investigator to asses the value of clinical data in diagnosis and follow up of CD in relation to investigational tools.

Patients and methods

A prospective study conducted at private clinic in Mosul city during the period from 30th of October 2007 to 30th of April 2011. Patients selected in the study were aged more than 6 months and on gluten containing diet, with various combinations of symptoms and signs suggestive of CD including chronic diarrhea, abdominal distention, offensive stool, anorexia, positive family history of CD in first degree relative, anemia defined according to

age and sex related hemoglobin levels and failure to thrive (FTT) defined as weight <5th centile for age and sex.

A total of 57 patients (39 males, 18 females) with mean age of 56.1 months, were evaluated by history and physical examination. They were screened by serological testing using second generation ELISAs IgA human recombinant tissue transglutaminase antibody (IgA anti tTG2) which was done by commercially available kit (AESKULISA tTG-A 3503/ Germany). Esophagogastroduedinoscopy and biopsy was done in Alsalam General Hospital in Mosul city where three sites of duodenum were biopsied from every patient. Biopsy specimens were evaluated in the same hospital and pathology reports were analyzed according to Marsh criteria [4].

Patients were reevaluated 6 months after GFD by weight measurements and same serological test.

Verbal consents were approved regarding clinical, hematological testing along with written informed consents were taken from parents of all children before endoscopic duodenal biopsy. The ethical committee approved this study.

Data analysis was done using SPSS program. Chi squared test was used for measurement of statistical significance.

Results

A total of 29 (50.9%) out of 57 symptomatic patients [18 males (62.1%) and 11 females (37.9%)] demonstrated positive biopsy results consistent with CD diagnosis; whereas the remaining 28 (49.1%) cases had normal biopsy results. Although 66.7% of patients with positive family history and 85.7% of patients with dimorphic anemia had positive biopsy of CD, all the studied clinical variables were not significantly associated with biopsy results (Table 1).

Table (1): Sensitivity, specificity, predictive values, accuracy and significance of clinical variables suggestive of CD in comparison to results of duodenal biopsy.

VARIBLE		Total	Biopsy of studied cases				Sensitivity %	Specificity%	+ve predictive value	-ve predictive value	Accuracy	P-VALUE*
			POSITIVE		NEGATIVE							
			No.	%	No.	%						
Symptoms												
Chronic diarrhea		38	17	44.7	21	55.3	59	25	44.7	36.8	42.1	0.190
Offensive stool		42	23	54.8	19	45.2	79.3	32.1	54.8	60	56.1	0.326
Abdominal distension		46	24	52.2	22	47.8	82.8	21.4	52.2	54.4	52.6	0.689
Anorexia		41	19	46.3	22	53.7	65.5	21.4	46.3	37.5	43.9	0.273
Family history	Positive	6	4	66.7	2	33.3	13.7	92.8	66.7	51	52.6	0.413
	Negative	51	25	49	26	51						
Signs												
Failure to thrive		48	25	52.1	23	47.9	86.2	17.9	52.1	55.6	52.6	0.674
Anemia		50	24	48	26	52	82.8	7.1	48	28.6	45.6	0.246
Hypochromic microcytic anemia		41	18	43.9	23	56.1	62.1	17.9	43.9	31.3	40.4	0.092
Dimorphic anemia		7	6	85.7	1	14.3	21.4	96.4	85.7	55.1	57.9	0.079
Macrocytic anemia		1	0	0	1	100	0	96.4	0	48.2	47.4	0.305
Normochrmic normocytic		1	0	0	1	100	0	96.4	0	48.2	47.4	0.305

*P- value: value less than 0.05 is considered significant.

Clinical features of studied patients with positive biopsy of CD showed that FTT was noticeable in 25 (86.2%) of patients followed by anemia, abdominal distension, and offensive stool in decreasing frequency. In 17 patients (58.6 %) who had CD had chronic diarrhea (Table 2).

IgA anti- tTG2 test was above the cut-off value of the used kit for a positive result which is more than 15 U/ml in 29 (50.9%) patients; all of them demonstrated a positive biopsy result suggestive of CD. On the other hand those with normal biopsy results had negative serological values.

Marsh type 3 histological grading was evident in 27 (93.1%) patients whereas Marsh type 1 grade was displayed in 1 (3.45%) case and Marsh type 2 grades in the other (Table 3).

Follow up of CD cases 6 months after GFD showed that catch up of weight was not achieved in 10 (43.5%) out of 23 CD patients with FTT whose (IgA anti tTG2) otherwise became normal. The remaining 2 CD patients with FTT had failure of catching up of weight, failure of serological normalization in conjunction with unchanging Marsh type 3 histological grading on repeated biopsy.

Table (2): Clinical features of 29 patients with positive biopsy of celiac disease.

Patients with positive biopsy of CD Cases (n=29)			
Variables		No.	%
Symptoms			
Chronic diarrhea		17	58.6
Normal bowel motion		12	41.4
Offensive stool		22	75.9
Abdominal distension		23	79.3
Anorexia		19	65.5
Positive family history		4	13.8
Signs			
Failure to thrive		25	86.2
Edema		1	3.4
Anemia		24	82.8
	Hypochromic microcytic	18	62.1
	Dimorphic	6	20.7

Table (3): Clinical features of 29 celiac disease cases in relation to histopathological grading.

Variable	Total	Patients with positive biopsy of CD Cases (n=29)						P- value*
		Marsh 1 1 (3.45%)		Marsh 2 1 (3.45%)		Marsh 3 27 (93.1%)		
		No.	%	No.	%	No.	%	
Symptoms								
Chronic diarrhea	17	0	0	1	5.9	16	94.1	0.257
Offensive stool	23	1	4.3	1	4.3	21	91.3	0.697
Abdominal distension	24	1	4.2	1	4.2	22	91.6	0.903
Anorexia	19	1	5.3	1	5.3	17	89.4	0.481
Positive family history	6	0	0	0	0	4	66.7	0.776
Signs								
Failure to thrive	25	0	0	1	4	24	96	0.109
Edema	1	0	0	0	0	1	100	0.957
Hypochromic microcytic anemia	18	0	0	1	5.6	17	94.4	0.140
Dimorphic anemia	6	0	0	0	0	6	100	0.411

*P- value: value less than 0.05 is considered significant.

Discussion

In 29 (50.9%) of studied cases, the diagnosis was correct based on clinical data, the positive predictive values of the majority of selected variables ranged approximately between (44%-54%) as an indicative of celiac disease diagnosis based on clinical manifestation. These findings support the recommendations of (NASPGHAN) [8], signifying the value of history and examination in selecting symptomatic patients for screening for CD. It has been estimated that the prevalence of celiac disease in children between 2.5 and 15 yr in the general population ranges from 3 to 13/1,000 children or ≈1/300 to 1/80 children [1], screening of patients with symptoms of celiac disease resulted in increase detection of CD from 3-13/1,000 children in the general population to 50.9% according to this study.

The diagnosis of celiac disease on the basis of clinical features alone was incorrect in 28(49.1 %) studied cases, similar results have been observed in other studies which showed that a clinical diagnosis in children on the basis of gastrointestinal symptoms alone was incorrect in more than 50% of cases [11-12], signifying that diagnosis and lifelong GFD treatment is not justifiable relying on clinical diagnosis alone.

The male: female ratio of the children with CD was 3:2 in the study done by Ujjal et al [13], which is similar to the present study results.

Although the sensitivity of some variables (offensive stool, abdominal distention, FTT and anemia) was high (close or over 80%) their specificity was low (around 20%), furthermore the studied clinical variables were not significantly associated with biopsy results (p-value >0.05), these may be explained by the fact that these clinical variables are common shared manifestations of other diseases that CD should be differentiated from [3].

In (58.6%) of studied CD patients had chronic diarrhea, comparable results were present in other studies [14-15]. In 41.4% of celiac cases in this study had normal bowel motion, Telega et al found that 28.2% of his cases had diarrhea and 5.1% had constipation suggesting that the remaining 66.7% had normal bowel motion [16], indicating that normal bowel motion does not preclude the possibility of CD diagnosis. Offensive stool was the compliant of (75.9 %) of our celiac disease patients compared to 50% in other study [1] which might be related to the severity and extent of mucosal damage. Abdomen was distended in (79.3 %) of studied CD patients, similar results (80%) were found by Khuffash et al [5]. Anorexia presented in two thirds of our cases which are concordant with the finding in other studies [1, 17].

Kuloğlu et al in Turkey observed failure to thrive in 34.8% of cases of CD [18] and Telega et al in Southeastern Wisconsin found that 25.4% of cases with CD presented with FTT [16]. While FTT was reported in 100% of cases with CD in Arabic studies conducted by Al-Hassany et al in Iraq[19], Khuffash et al[5] in Kuwait and Al-Tawaty et al in Libya[20], FTT reported in 91% of CD patients in India[21]. In our study (86.2%) of CD cases present with FTT. This high frequency of FTT may be attributed to delayed diagnosis, severity of mucosal damage with malabsorptive consequences or concomitant malnutrition. Less common presentations of celiac disease include hypoproteinemia[22], secondary to protein-losing enteropathy[7] manifested by edema which was evident in 3.4 % of studied patients.

Rashid et al found that 8% of the children had a first-degree relative with biopsy-confirmed celiac disease [23], while family history was positive in 21% in the study conducted by D'Amico et al in USA [24]. In our study positive family history was found in (13.8%) of cases, similar result was found by Barker et al [7]. This difference may be attributed to the heterogeneity of the studied populations, subject selection, different genetic susceptibility and rate of consanguineous marriages. Positive family history was the positive predictor of CD diagnosis in 66.7% of cases before the diagnosis was histologicaly confirmed, having specificity of 92.8%. The result found in our study supports the routine testing of asymptomatic children who are first-degree relatives of confirmed celiac disease recommended by (NASPGHAN).

Anemia is still a common presentation of celiac disease [25]. Hypochromic microcytic

morphology was the most frequent type associated with CD cases in this study , which is concordant with the finding in other studies [14,16,17]. In 43.9% of cases in this study hypochromic microcytic anemia was among the presenting findings leading to the diagnosis of celiac disease, similar result was found in Greek by Karyda et al [26] and in Basrah by Mansoor et al [27]. Whereas higher results were found by Hashim et al [28], this may be related to the sample selection and time of diagnosis. Overall all these results support the recommendations of (NASPGHAN) that persistent iron deficiency anemia is an indication for celiac screening [4]. Dimorphic anemia was present in 20.7% of studied cases with celiac disease and Patwari et al also found that 20% of CD had dimorphic anemia [29] nevertheless it was the foreteller of the diagnosis in 85.7% of studied cases as a positive predictor of CD before biopsy results appeared and having a specificity of 96.4%. These high values may be related to the severity of mucosal injury in view of the fact that all studied patients with dimorphic anemia had Marsh 3 histopathological grading.

Overall, the severity of symptoms associated with celiac disease is highly variable, and in large part this reflects the severity and extent of mucosal damage [3], which explain the more frequent symptoms in our patients with Marsh 3 histopathological changes. The reported prevalence of GI manifestations has varied widely among different studies; this may be due to the low number of patients evaluated or a delay in their presentation [30].

Catch-up growth is characterized by an increased growth velocity in height and/or weight after the removal of some constraint on normal growth, this increased velocity brings a child's height-for-age or weight-for-age status back toward the normal centiles[31]. Treatment with GFD did not result in an overall significant increase in weight-for-height score up to 4 years of follow-up [32]. Mean weight-for-height returned to normal 15 months after dietary treatment [33]. Failure of the anti- tTG level to decline over a period of 6 months after starting the GFD suggests continued ingestion of gluten or related products [4]. Catch up of weight was not achieved in 10 (43.5%) out of 23 enrolled CD patients with FTT whose (IgA anti tTG2) normalized after 6 months of GFD, indicating that catch up of weight may be delayed, cannot be relied upon as an early marker of clinical improvement in patients with proven adherence to GFD manifested by normal serological monitoring as well as in patients on trail of GFD without disease confirmation.

The result of this study albeit reflecting private clinic statistics, evidently illustrated that celiac disease manifestations is a useful tool to initiate an effective serological screening tests rather than a tool to label a diagnosis and permanently treat assumed celiac disease without based evidence ,along with erroneous follow up of manifestation rather than the disease. As in no case should false information given to the patient, this study notify a doctor about percentages of incorrect decisions made depending only on clinical experience of CD, which ultimately affect patient health in addition to its impact on social, financial and psychological aspects of patient life and also reflects the ethical and medical responsibility of the doctor toward his patient aiming to give optimum quality of available medical care. The result of this study emphasizes the importance of the patient human rights to get an evidently based accurate diagnosis of celiac disease before permanent changing of dietary life style.

References

1. Sood MR. Disorders of malabsorption in Nelson Textbook of Pediatrics, by Kliegman RM, Behrman RE, Hal BSJ, Bonita F. 18th ed. Philadelphia: Saunders Elsevier 2007; 1591-1593.
2. Hariza MB, Kallel-Sellamie M, Kallelb L, Lahmerc A, Haliouia S, Bouraouic S, *et al*. Prevalence of celiac disease in Tunisia: mass-screening study in schoolchildren. European Journal of Gastroenterology & Hepatology 2007;19:687–694
3. Murphy MS, Walker WA. Celiac disease. Pediatr. Rev 1991; 12: 325-330
4. Nusier MK, Brodtkorb HK, Rein SE, Odeh A, Radaideh AM, Klungland H. Serological screening for celiac disease in

schoolchildren in Jordan. Is height and weight affected when seropositive? Ital J Pediatr 2010 Feb 9; 36:16.
5. Khuffash FA, Barakat MH, Shaltout AA, Farwana SS, Adnani MS, Tungekar MF. Coeliac disease among children in Kuwait: difficulties in diagnosis and management. Gut 1987; 28:1595–1599.
6. Hung JCC, Phillips AD, Walker-Smith JA. Coeliac disease in children of West Indian origin? Archives of Disease in Childhood 1995; 73: 166-167.
7. Barker CC, Mitton C, Jevon G, Mock T. Can tissue transglutaminase antibody titers replace small-bowel biopsy to diagnose celiac disease in select pediatric populations? Pediatrics 2005; 115: 1341-1346.
8. Hill ID, Dirks MH, Liptak GS, *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: 1–19.
9. Walker-Smith JA, Guandalini S, Schmitz J, Schmerling DH, Visakorpi JK. Revised criteria for diagnosis of coeliac disease: Report of working Group of European Society of Pediatric Gastroenterology and Nutrition. Arch Dis Child. 1990; 65:909–991.
10. Baudon JJ, Johanet C, Absalon YB, Morgant G, Cabrol S, Mougenot JF. Diagnosing celiac disease: a comparison of human tissue transglutaminase antibodies with antigliadin and antiendomysium antibodies. Arch Pediatr Adolesc Med. 2004; 158:584-588.
11. Paerregaard A, Vilien M, Krasilnikoff PA, Gudmand-Hoyer E. Supposed coeliac disease during childhood and its presentation14–38 years later. Scand J Gastroenterol 1988; 23:65–70.
12. Stenhammar L. Transient gastro-intestinal disorders during infancy and early childhood: a follow-up study with special reference to coeliac disease. Acta Paediatr Scand 1981;70:383–387.
13. Ujjal Poddar, Babu Ram Thapa, Kartar Singh. Clinical features of celiac disease in indian children: are they different from the west? J Pediatr Gastroenterol Nutr 2006 September; 43: 313-317.
14. Rawashdeh MO, Khalil B, Raweily E. Celiac disease in Arabs. J Pediatr Gastroenterol Nutr 1996; 23:415–418.
15. Elsurer R, Tatar G, Simsek H, Balaban YH, Aydinli M, Sokmensuer C. Celiac disease in the Turkish population. Dig Dis Sci 2005; 50:136–142.
16. Telega G, Bennet TR, Werlin S. Emerging new clinical patterns in the presentation of celiac disease. Arch Pediatr Adolesc Med 2008; 162(2):164-168.
17. Demir H, Yüce A, Koçak N, Ozen H, Gürakan F. Celiac disease in Turkish children: presentation of 104 cases. Pediatr Int 2000 Oct;42(5):483-487.
18. Kuloğlu Z, Kirsaçlioğlu CT, Kansu A, Ensari A, Girgin N. Celiac disease: presentation of 109 children. Yonsei Med J 2009 Oct 31; 50(5):617-623.
19. Al-Hassany M. Coeliac disease in Iraqi children. J Trop Pediatr Environ Child Health 1975; 21:178–179.
20. Al-Tawaty AI, Elbargathy SM. Coeliac disease in north-eastern Libya. Ann Trop Paediatr 1998; 18:27–30.
21. 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 Sep; 43(3): 313-317.
22. Green HRP, Cellier C. Celiac disease. N Engl J Med 2007; 357:1731–1743.
23. Rashid M, Cranney A, Zarkadas M, Graham ID, Switzer C, Case S, *et al*. Celiac Disease: Evaluation of the Diagnosis and Dietary Compliance in Canadian Children Pediatrics 2005; 116: e754-e759.
24. D'Amico MA, Holmes J, Stavropoulos SN, Frederick M, Levy J, DeFelice AR, *et al*. Presentation of pediatric celiac disease in the united states: prominent effect of breastfeeding. Clin Pediatr (Phila) 2005; 44; 249.

25. Harper JW, Holleran SF, Ramakrishnan R, Bhagat G, Green PHR. Anemia in celiac disease is multifactorial in etiology. Am. J. Hematol 2007; 82:996–1000.
26. Karyda S, Mouskou S, Avgoustidou P, *et al*. The clinical spectrum of celiac disease in Greek children – a single center experience. J Pediatr Gatroenterol Nutr 2004; 39: 222 (Abstract).
27. Mansoor AA, Strak SK. Prevalence of celiac disease among patients with iron deficiency anemia: Personal experience and review of literature. Pak J Med Sci October-December 2005 Vol. 21 No. 4 413-416.
28. Hashim AR, Abdulwahid R. Iron deficiency anemia as a sole presentation of gluten sensitive enteropathy. Med J Basrah University 2003; 21:120-124.
29. Patwari AK, Anand VK, Kapur G, Narayan S, Clinical and nutritional profile of children with celiac disease. Indian Pediatr 2003; 40(4):337-342.
30. Barada K, Bitar A, Mokadem MA, Hashash JG, Green P. Celiac disease in Middle Eastern and North African countries: A new burden? World J Gastroenterol 2010 March 28; 16(12): 1449–1457.
31. Crowther NJ, Cameron N, Trusler J, Toman M, Norris SA, I Gray P. Influence of catch-up growth on glucose tolerance and cell function in 7-year-old children: results from the birth to twenty study. Pediatrics 2008; 121: e1715-e1722.
32. Patwari AK, kapur G, satyanarayana L, Anand Vk, Jain A, Gangil A, *et al*. Catch-up growth in children with late-diagnosed coeliac disease. Br J Nutr 2005 Sep; 94(3):437-442.
33. Damen GM, Boersma B, Wit JM, Heymans HS. Catch-up growth in 60 children with celiac disease. J Pediatr Gastroenterol Nutr 1994; 19(4):394-400.

