Pattern of celiac disease in a sample of Iraqi children

Dr. Kifah Hamdan Abdul Ghafoor¹, Dr. Maher Mohamed Hassan², Dr. Wael Waggh Saeed³

¹M.B, Ch.B, DSP, PhD (pathology)
²AL-Akori M.B.Ch.B,DCH,FICSM (ped)
³M.B.Ch.B.D.CH

ABSTRACT:

Background: Celiac Disease (CD) presentation pattern is changing over the years with its diagnostic criteria and different types of Celiac Disease is emerging.

Objectives: To evaluate CD cases in a sample of Iraqi clinically, serologically & histopathologically and to spot any atypical cases.

Patients and methods: Forty children diagnosed as Celiac Disease by positive serology were referred to the outpatient department of children Welfrare Teaching Hospital & GIT center in Baghdad for further evaluation in the period from first of April 2011 till the first of Jan.2012 were studied. The clinical presentation, serological tests and histopahtological findings were recorded and analyzed.

Results: Out of the 40 patients who had positive serology tests, 26 patients only (65%) had positive duodenal biopsy of CD, 9 of the 26 patient cases (34.6%) had GIT symptoms, the rest 17(65.4%) had non GIT symptoms (12 had type 1 Diabetes Mellitus, 3 with isolated short stature & 2 cases had thyroid problems). Constipation, abdominal pain & offensive stool were more significant findings than the usual diarrhea and abdominal distention in the cases presented with GIT symptoms. Height for age in 96.2% of them was -SD below the mean. Weight/height in (76.9%) & (54%) of the BMI were -2SD below the mean. Anti Endomyseal IgA antibodies was 14 cases (35%) with positive serology and negative duodenal biopsy result.

Conclusion: The pattern of CD is changing with atypical clinical presentations and CD presents in a non gastrointestinal symptoms in about two third of the cases. Latent CD was found in one third of cases. Anti Endomyseal antibody was the most sensitive and specific serological marker in this study.

Key wards: Celiac Disease.

Introduction

Celiac disease (CD) is an immune mediated inflammatory condition of the small bowel mucosa caused by a permanent sensitivity to ingested gluten cereals such as wheat, rye, and barley. Although oat toxicity is still contentious, there is emerging evidence that a long-term oat-free diet is probably not necessary (1-3). The prevalence of celiac disease in the United States, Europe, and the United Kingdom is between 0.75% and 1%. (4-7) Reports of a high prevalence of celiac disease in Egypt(8) and in Tunisia(9) indicate that disease is also common in the Arab population, it has been shown that celiac disease is common in developing countries where the major staple diet is wheat (2). The diagnosis of celiac disease is based on the 2011 European Society of Pediatric Gastroenterology and Nutrition criteria which is based on symptoms, positive serology, and histology that is consistent with CD but if immunoglobulin A anti-tissue transglutaminase type 2 antibody titers are high (>10 times the upper limit of normal), then the option is to diagnose CD without duodenal biopsies by applying a strict protocol with further laboratory tests, also the diagnosis of CD is based on positive serology and histology. HLA-DQ2 and HLA-DQ8 testing is valuable because CD is unlikely if both haplotypes are negative (10). Most countries have experienced a changing CD symptom pattern over the years. The so-called classic/typical CD presenting with a malabsorption syndrome in childhood is less frequent. It is increasingly common to diagnosis children who have subtle or non gastrointestinal symptoms (11). In fact, symptomatic cases (10%) are considered to be the tip of the iceberg, some apparently asymptomatic patients have manifest mucosal changes which are normalized on a GFD. These subjects are considered to have silent CD. In addition, there are individuals in whom the mucosal changes of CD have not developed despite celiac serology. These individuals can be considered to have latent or potential CD. Thus, the clinical presentation of CD can be likened to an iceberg in which the tip represents symptomatic cases (silent, latent or atypical) (12).
Aim of the study

This descriptive study was done:
14. To evaluate the cases of celiac disease, clinically, serologically and histopathologically.
15. To have an idea about pattern of celiac disease and the presence of atypical cases in our setting.
16. To find out the best approach for the diagnosis of celiac disease in children.

Patients and methods

The study was a prospective cross-sectional study done at the gastrointestinal (GIT) outpatient clinic of the Children Welfare Teaching Hospital (CWTH) and the GIT hospital in the Medical City complex in Baghdad. The data collection was carried out for three hours a day, three days a week over the period from the first of April 2011 till the first of Jan. 2012. The study included 40 patients with diagnosis of CD presented either for follow up or presented during the collection of data. Some presented with gastrointestinal symptoms or non gastrointestinal symptoms like (short stature or failure to grow) or the high risk groups (other immune disorders) for screening. Evaluation of the clinical symptoms, different serological tests and upper intestinal biopsy were done to those cases. Weight, length/height and BMI (body mass index) of all cases were recorded and compared to their standard according to the WHO standard. (67) No staging was done for the histopathological findings of the duodenal biopsy in our labs. But villous atrophy of different stages with mononuclear cells infiltration and increase intraepithelial lymphocytes and deepening of crypts were considered the cornerstone for the diagnosis of CD. (68) Few patients only had total IgA level.

Statistical Analysis

Statistical packages SPSS18 (Statistical Package for Social Sciences version 18) and epicalc 2000 use for data input and analysis. Continuous variables presented as mean and standard deviation (SD) and discrete variables presented as numbers and percentages. Chi square test for independence and Fisher's exact test used as appropriate to test the significance of association between discrete variables and chi square test for goodness of fit used to test the significance of observed distribution (trend). Findings with P value equal to or less than 0.05 were considered significant. Screening test performance produced with their 95% confidence intervals (95%CI)

Results

The study included 40 children (22 males and 18 females) with clinical features suggestive of celiac disease, their ages varied from 11 to 170 months with an average of 85.3± 54.2 months and the duration of complaints varied from 3 to 120 months with an average of 19.2± 19.8 months (table 1). Concerning the age at which the gluten was introduced to the diet was 8.0± 3.4 months, minimal duration was 3 months and maximum duration was 18 months (table 1). Twenty six (65.0%) child were diagnosed as celiac disease with positive biopsy (figure 1).

Table 1: Descriptive statistics for age of involved children, the duration of their symptoms and the duration before introduction of gluten containing diet.

<table>
<thead>
<tr>
<th>Variable</th>
<th>N</th>
<th>Minimum</th>
<th>Maximum</th>
<th>Mean</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (month)</td>
<td>40</td>
<td>9</td>
<td>170</td>
<td>85.3</td>
<td>54.2</td>
</tr>
<tr>
<td>Duration of symptoms (month)</td>
<td>40</td>
<td>3</td>
<td>120</td>
<td>19.2</td>
<td>19.8</td>
</tr>
<tr>
<td>Age at which the gluten was</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>introduced to the diet</td>
<td>40</td>
<td>3</td>
<td>18</td>
<td>8.0</td>
<td>3.4</td>
</tr>
</tbody>
</table>

Table 2: Demographic characteristics of study sample.

<table>
<thead>
<tr>
<th>Demographic Characteristics</th>
<th>Result of biopsy</th>
<th>Not</th>
<th>Total</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Celiac</td>
<td>(N %)</td>
<td>N(%)</td>
<td>N(%)</td>
<td></td>
</tr>
<tr>
<td>Male Gender</td>
<td>15(57.8)</td>
<td>7(53.8)</td>
<td>22(65.4)</td>
<td>0.819</td>
</tr>
<tr>
<td>Urban settings</td>
<td>24(92.3)</td>
<td>13(92.9)</td>
<td>39(92.5)</td>
<td>0.950</td>
</tr>
<tr>
<td>Positive family history of celiac</td>
<td>3(11.5)</td>
<td>3(21.4)</td>
<td>6(15.0)</td>
<td>0.646</td>
</tr>
<tr>
<td>Consanguinity of parents</td>
<td>18(69.2)</td>
<td>7(50.0)</td>
<td>25(62.5)</td>
<td>0.231</td>
</tr>
</tbody>
</table>
The pure gastrointestinal symptoms presented in 9 cases (34.6%). Table 3 showed that the insulin dependent diabetes (IDDM) found in 12 (46.2%); the contribution to this high proportion was statistically significant (p<0.05). Isolated short stature had been reported in 3 (11.5%) which was nonsignificant association observation (p>0.05). Concerning the remaining patients who had overlap symptoms (gastrointestinal symptoms), the observation of 13 (50.0%) with abdominal distension and 9 (34.6%) of patients to have frequent bowel motion and vomiting in 3 (11.5%) were non significant in this study (p>0.05,table 3). However constipation in one case (4.0%), abdominal pain 4 (15.4%) and offensive stool 5 (19.2%) found a significant association with biopsy results (p<0.05,table 3).

Anthropometric assessment of celiac patients:
In 20 patients (76.9%) the weight for length/height were less than two standard deviation (below the mean), 18 patients 69.2% had length/height for age below two standard deviations, and 22 cases 84.6% found to have BMI for age less than two standard deviation than medians (p<0.05,table 4).

Table 3: Clinical presentation of celiac patients diagnosed with biopsy.

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>N = 26 (100%)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pallor</td>
<td>0(0.0)</td>
<td>-------</td>
</tr>
<tr>
<td>Frequent bowel motion</td>
<td>9(34.6)</td>
<td>0.117</td>
</tr>
<tr>
<td>constipation</td>
<td>1(4.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>4(15.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Abdominal distension</td>
<td>13(50.0)</td>
<td>1.000</td>
</tr>
<tr>
<td>vomiting</td>
<td>3(11.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Offensive stool</td>
<td>5(19.2)</td>
<td>0.002</td>
</tr>
<tr>
<td>Short stature</td>
<td>6(15%)</td>
<td>1.000</td>
</tr>
<tr>
<td>Non-gastrointestinal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&amp; high risk group</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Isolated short stature</td>
<td>3(11.5)</td>
<td>0.214</td>
</tr>
<tr>
<td>Insulin dependent</td>
<td>12(46.2)</td>
<td>0.011</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td></td>
<td></td>
</tr>
<tr>
<td>thyroiditis</td>
<td>2(7.7)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Note: there is an overlap

Table 4: Anthropometric measurement of celiac patients diagnosed with biopsy.

<table>
<thead>
<tr>
<th>Demographic Characteristics</th>
<th>N</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight for length/height &lt;-2SD</td>
<td>20(76.9)</td>
<td>0.006</td>
</tr>
<tr>
<td>Height/length for age &lt;-2SD</td>
<td>18(69.2)</td>
<td>0.050</td>
</tr>
<tr>
<td>BMI for age &lt;-2SD</td>
<td>22(84.6)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Screening with serology
With reference to table 5 (figures 3-9):

- Clinical characteristic expressed very difficult performance if used as screening tests, since SN(58%) and very poor SP(7%), in the same time, it’s showed very low PPV(54%) and NPV(8%).
- Anti endomyseal IgA: was showed in excellent SN and SP in the same time, the predictive value was good (88%) and excellent NPV(100%).
- Anti endomyseal IgG: both SN and NPV were poor (50%) while both SP and PPV were of moderate performance (67%).
- Anti tTG IgA: exhibited a good SN and PPV were good (84%) but poor SP and NPV (40%).
- Anti tTG IgG: both SN and PPV were good (85%) but both SP and NPV were of low value (50%).
- Anti gliadin IgA: moderate SN (67%) but all of SP, PPV and NPV were (20,53,33)% respectively.
- Anti gliadin IgG: the sensitivity of moderate value (64%) and all other indices were of low value (SP 0%, PPV 47%, NPV 0%).
- Anti reticulin: showed very low performance for all indices (SN 33%, SP 0% and NPV 0%).
- In general IgG serologic tests showed weaker performance than IgA test.
- Although not all patients had total IgA levels, the high titer of IgA levels in all serological tests indicate indirectly that there was no case with deficient total IgA level especially the anti endomyseal IgA levels and the anti tTG antibodies.

Table 5: Performance of different tests in the detection of celiac cases

<table>
<thead>
<tr>
<th>Method</th>
<th>Positive Readings</th>
<th>SN [95%CI]</th>
<th>SP [95%CI]</th>
<th>PPV [95%CI]</th>
<th>NPV [95%CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical Diagnosis</td>
<td>15/40</td>
<td>0.58</td>
<td>[0.97,0.76]</td>
<td>0.07</td>
<td>[0.00,0.36]</td>
</tr>
<tr>
<td>Endomyseal IgA</td>
<td>7/10</td>
<td>1.00</td>
<td>[0.66,0.99]</td>
<td>0.67</td>
<td>[0.07,0.83]</td>
</tr>
<tr>
<td>Endomyseal IgG</td>
<td>2/7</td>
<td>0.50</td>
<td>[0.09,0.91]</td>
<td>0.67</td>
<td>[0.09,0.91]</td>
</tr>
<tr>
<td>Antitissue Transglutaminase IgA</td>
<td>16/24</td>
<td>0.84</td>
<td>[0.60,0.96]</td>
<td>0.40</td>
<td>[0.07,0.83]</td>
</tr>
<tr>
<td>Antitissue Transglutaminase IgG</td>
<td>4/7</td>
<td>0.80</td>
<td>[0.20,0.99]</td>
<td>0.60</td>
<td>[0.33,0.97]</td>
</tr>
<tr>
<td>Anti gliadin IgA</td>
<td>8/21</td>
<td>0.67</td>
<td>[0.35,0.99]</td>
<td>0.65</td>
<td>[0.04,0.90]</td>
</tr>
<tr>
<td>Anti gliadin IgG</td>
<td>7/19</td>
<td>0.64</td>
<td>[0.32,0.80]</td>
<td>0.47</td>
<td>[0.01,0.40]</td>
</tr>
<tr>
<td>Antireticulin</td>
<td>2/10</td>
<td>0.33</td>
<td>[0.06,0.76]</td>
<td>0.33</td>
<td>[0.02,0.69]</td>
</tr>
</tbody>
</table>
Sensitivity (SN), specificity (SP), positive predictive value (PPV), negative predictive value (NPV).

Figure 2: Evaluation of clinical diagnosis of celiac disease compared to diagnosis with biopsy.

Figure 3: Performance of endomyseal IgA as a screening test.

Figure 4: Performance of endomyseal IgG as a screening test for celiac disease.

Figure 5: Performance of anti tissue transglutaminase IgA as a screening test for celiac disease.

Figure 6: Performance of anti tissue transglutaminase IgG as a screening test for celiac disease.

Figure 7: Performance of anti gliadin IgA as a screening test for celiac disease.
Discussion

Celiac disease (CD) is a permanent intolerance to ingested gluten that results in immunologically mediated inflammatory damage to the small intestinal mucosa. CD must always be considered when dealing with children manifesting growth failure. Usually atypical presentation is seen in older children, who often have no overt features of malabsorption. (69) Extra-intestinal manifestation such as short stature, delayed puberty, dental enamel defects, and arthralgia may occur as a monosymptomatic manifestation. (70) The oldest patients in this study was 170 months (14.1) years, the mean age (SD) was 85.3 months (7) years which was younger than the CD cases in the Saudi study which was 9.6 years.(71) In the Jordanian study the mean age of presentation was 4.6 years. (72) Some of the family trend is to introduce the gluten earlier than 6 months which may lead to misdiagnosis of CD with food allergy as the youngest age in this study to introduce gluten was 3 months.

The delay in the diagnosis of CD (average of 19.2 months) was probably because of prolonged breast feeding and the average age to introduce gluten in this study by history was eight months. Other infectious causes of persistent diarrhea which result in malnutrition might mimic CD cases and delay the diagnosis of celiac disease in our country. In this study the female to male ratio was 1:1.37. In the recent Saudi study the female to male ratio was 1.22:1 (71) and in an old Jordanian study the female to male ratio was 1.83:1. (72) Classically infants with CD present with impaired growth, diarrhea and abdominal distension, the gastrointestinal symptoms are typically anorexia, vomiting, chronic diarrhea and abdominal distension. (68,69) Those symptoms proved to be non significant in relation to our CD patients but constipation, abdominal pain and offensive stool were of significant value although they were not the classical presentations.

In Rawashda study diarrhea was present in 9 (34.6%), abdominal distension in 13 (50%). (72) Non-gastrointestinal symptoms cases and the high risk group, celiac disease was present in 17 (52%) of cases in this study which agree with Saudi study where 51% of cases registered during screening of high risk group. (71) Failure to grow and short stature are a well known results of the delay in the diagnosis of CD. Isolated short stature was the presentation in 3 (11.5%) of cases in this series. The short stature presentation found as a sole referral cause in (12%) in Rawashda study (72) and in 10.9% of the Saudi study with typical duodenal biopsy and in 4.3% in potentially CD cases with mild villous atrophy. (73) The prevalence of CD reported among children with type I Diabetes Mellitus(DM) in 26 reports varied from 0.97% to 16.4%. (74) In our study 46.2% of our CD cases were diabetics with some difficulties in the control. Those patients could benefit from GFD for the metabolic control and also improving their growth. (71) There is no local study yet to know the incidence of CD in the diabetic children in Iraq. There was a significant association of two cases of autoimmune Thyroiditis presented to the clinic proved to have positive biopsy finding. Children with CD have an increased prevalence of autoimmune thyroid diseases even after being on a gluten free diet, making it important to screen for thyroid disease at follow up. (68)

Growth failure due to nutrient maladsorption or anorexia is one of the important manifestation of CD. ( 75) In our study 20(76.9%) of CD cases had low weight for length/height by -2SD which is very high number comparing to the Saudi children where 35% only found to be under weight and only 38% had short stature. The BMI in our patients was -2SD in 22(84.6%) versus 23% in the Saudi children. (71) The criteria for the diagnosis set by ESPGHAN in Dec.2011 & published ahead of print suggested that duodenal biopsy is optional if IgA anti tTG type 2>10 times the upper limit of normal or positive HLA-DQ2 & or HLA-DQ8 in a positive serology & histology. (7)
Because of the unavailability of type 2 IgA anti tTG antibody and the haplotypes in our setting, we were left with the suggestive clinical symptoms, the available serology tests and duodenal biopsy results. Although not all different screening tests were done to all patients but the IgA anti EM antibodies proves to have high sensitivity (100%) and moderate specificity (67%) more than IgA anti tTG which shows sensitivity (84%) and specificity (40%), those results did not agree with IgA EMA (76,77) this may be attributed to the small sample taken in a single center only. Despite the high accuracy of anti EMA and anti tTG, seronegative celiac disease still occurs. For this reason duodenal biopsy in patients with a high suspicion of celiac disease still is recommended even if the serologic testing is negative. (78)  

All our patients which we can label them as having typical CD had positive serology but only 26(65%) had positive biopsy. Fourteen of cases (35%) had positive serology and negative biopsy and could be labeled as latent CD. We can't have an idea about number of cases which had positive symptoms and negative serology because all our study group which were included in the study had positive serology. The classical typical CD cases with gastrointestinal symptoms were 9(34.6%) only.

Conclusions

Typical cases of CD presented in one third of cases and 2/3 of them with positive biopsy result had atypical clinical presentation.

1. Constipation, abdominal pain and offensive stool were more significant than other classical gastrointestinal symptoms.
2. One third of cases had positive serology with negative biopsy (latent cases).
3. Height in most of the patients was -2SD below the mean. Two third of CD patients had low weight for height/length and more than 3/4 of the patients BMI were -2SD below the mean for age.

References


44. Lewis NR, Scott BB. Systematic review: the use of serology to exclude or diagnose coeliac disease (a comparison of the endomysial and tissue transglutaminase antibody tests). Aliment Pharmacol Ther 2006;24(1):47-54.


68. A F Rodrigues, H R Jenkins. Investigation and management of celiac disease. adc.bmj. on September 4,2011- published by group.bmj.