Tropical Gastroenterology 2008.29;4:217–220

Report from the Tropics

Pattern of celiac disease in infants and children

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ABSTRACT

This study involved all children with celiac disease admitted and seen in the Paediatric Gastroenterology Clinic at King Khalid University Hospital (KKUH) over a 10-year period. In the first year, we identified 62 cases with celiac disease. Their mean age at presentation, introduction to cereals in the diet, and onset of symptoms were 6.5, 6 and 6 months, respectively, and most of the children belonged to the indigenous population. There were three families with more than one affected child and most families were of good social status. The main symptoms noted were diarrhoea in 34 (57%), growth failure in 47 (74.6%), abdominal distension in 21 (33%), and vomiting in 14 patients (14%). The significant physical signs at the time of presentation were short stature, seen in 44 patients (69.8%), pallor in 25 (40.3%) and abdominal distention in 21 (33%). The mean haemoglobin, serum feritin, serum folate, calcium, and serum albumin were 10.25 g/dL, 2.49 g/mL, 0.25 ng/mL, 8.86 mg/dL, and 3.7 g/dL. The mean anti-reticulin IgG, anti-endomyseal IgG, IgA and anti-gliadin IgG, IgA were one in 246, 332, 720, 121 and 300 units. There was total villous atrophy in each patient at the time of initial presentation; repeat small bowel biopsies were done in 12 patients of whom 6, 4 and 2 had normal villi, partial villous atrophy and subtotal villous atrophy, respectively. A third biopsy was performed in 2 patients while on gluten containing diet, which revealed villous atrophy. Most of the children improved on gluten-free diet.

KEYWORDS: celiac disease, children, Saudi Arabia

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Introduction

Gluten-sensitivity enteropathy, also named celiac disease (CD), constitutes permanent intestinal intolerance to the dietary wheat constituent gliadin and related proteins that leads to the formation of intestinal lesions in the genetically susceptible individual. This condition has significant epidemiologic relevance; at a conservative estimate, the prevalence of gluten-sensitive enteropathy is 1 per 1000 population in the United States,[1] but it is now becoming clear that a greater proportion of individuals have clinically silent disease,[2,3] and probably many others have a minor form of the enteropathy.

Celiac disease is a major cause of protracted diarrhoea in Caucasian children.[3] However, there have been reports of its occurrence in non-Caucasian countries like Kuwait,[4] and India as well.[5] The purpose of this study is to look at the occurrence of celiac disease in Saudi Arabia and to consider it as a possible diagnosis in children with protracted diarrhoea.

Thus we aimed to study disease characteristics of all children with celiac disease admitted and seen in the Paediatric Gastroenterology Clinic at King Khalid University Hospital (KKUH) over a 10-year period.

Method

We reviewed the clinical charts of all children admitted to King Khalid University Hospital, Riyadh with a diagnosis of celiac disease over a 10-year period. The diagnostic criteria used belonged either to the old or to the revised criteria for the diagnosis of celiac disease,[6] the former, published in 1969, involves taking three small bowel biopsies, first at the time of initial presentation, second after the initiation of a gluten-free diet and third after a gluten challenge; the latter, published in 1989, involves obtaining a biopsy at the time of initial presentation, and monitoring clinical response to gluten free diet plus positive test of gliadin antibodies in children more than 2 years of age. The other data collected include anti-gliadin, anti-reticulin and anti-endomyoseal antibodies; all these tests were done by ELISA immunoassay.

Results

Sixty-two patients were identified during the study; all had small bowel biopsy carried out at initial presentation. Their mean age at presentation was 6.5 months (range 0.3 – 168 months), 22 were male (36%) and 40 were female (63%). 58 patients (93.5%) were Saudi Nationals and 4 patients (6.5%) were not. All patients had been delivered at full-term through normal vaginal delivery. Three families demonstrated positive consanguinity and had more than one affected child in the

same family. Most of the patients were of good social status; two patients were breast fed (3.6%) while 60 patients (96.4%) were on mixed feeding.The mean age of introduction to cereals was 6 months (range 4-8 months). The mean age at which symptoms started was 57.2 months, range 4-156 months.

The main symptoms of the patients were chronic diarrhoea in 34 (54%), vomiting in 14 (22.2%), abdominal pain in 11 (17.5) and constipation in 2 (3.2%). Growth failure was seen in 47 cases (74.6%) and abdominal distension in 21 (33.3%). (Table 1)

Table 1: The main symptoms at the time of presentation

Mode of Presentation	No. of Patients	%
Diarrhea	34	54
Vomiting	14	14
Growth Failure	47	74.6
Pallor	3	4.8
Abdominal Distension	21	33
Constipation	2	3.2
Abdominal Pain	11	17.5

The mean weight of the patient at the time of presentation was 16.7 ± 6.8 kg, and the mean height was 105.8 ± 6.81 cm. The main physical signs observed at the time of presentation were growth failure (both height and weight were well below the 5th percentile) in 47 (74.6%), pallor in 25 (40.3%), abdominal distention in 21 (33.3%), rickets in 6 (9.5%), wasting in 3 (4.8%), skin excoriation in 2 (3.2%), and isolated short stature in 17 (27.4%), respectively; none of the patients had oedema or angular stomatitis at the time of presentation. (Table 2)

Table 2: The main physical signs at the time of presentation

Findings on Presentation	No.	%
Pallor	25	40.3
Rickets	6	9.5
Wasting	3	4.8
Skin excoriation	2	3.2
Short Stature	17	27.4
Abdominal distension	21	33

Twelve patients (19%) had associated insulin dependent diabetes. Hypothyroidism, asthma and Down's syndrome were associated with CD in 4, 2 and 1 (6.3, 3.2, 1.6%) patients, respectively. (Table 3)

Table 3. Associated disease

Others Associated	No.	%
Disease		
Diabetes	12	19
Hypothyroidism	4	6.3
Asthma	2	3.2
Down Syndrome	1	1.6

The main laboratory data at the time of presentation (Table 4) included mean haemoglobin 10.25 g/dL (standard deviation (SD 1.72), mean serum iron 0.23 µg/dL ± SD (0.033) and mean serum feritin 2.49 ng/dL ± SD (3.97), mean serum folate 0.25 ng/mL ± SD (1.16), mean RBC folate 1.5 ng/mL ± SD (0.57), mean vitamin B_{12} 2.2 pg/L ± SD (0.11), mean calcium 8.86 mg/dL ± SD (0.22), mean phosphate 4.3 mg/dL ± SD (0.58) and mean alkaline phosphatase 311.5 U/L ± SD (231.42). The mean serum protein was 6.4 g/dL ± SD (0.99), mean serum albumin 3.7 g/dL ± SD (0.69), mean blood glucose 137.5 mg/dL ± SD (80), mean serum sodium 138 mεq/L ± SD (3.9), mean serum potassium 4.2 mεq/L ± SD (0.56) and mean serum magnesium 0.67 mg/dL ± SD (0.12). Small bowel aspirate demonstrated giardiasis in one patient. Stool was negative for reducing substance and positive for fat in three patients.

The mean anti-reticulin IgG antibody was one in 246 units ± SD (400) (normal value less than one in 20). The mean anti-endomyoseal IgG was one in 2332 units ± SD (653), mean anti-endomyoseal IgA was one in 720 units ± SD (560), mean anti-gliadin IgG was one in 121 units ± SD (147) and the mean anti-gliadin IgA was one in 300 units ± SD (898). (Table 5)

The mean serum immunoglobulin IgG was 1.26 mg/dL SD (0.65), mean serum immunoglobulin IgA was 0.29 mg/dL ± SD (0.10), mean serum immunoglobulin IgM was 0.98 mg/dL ± SD (0.06) and mean serum immunoglobulin IgE was 23.31 mg/dL ± SD (33) as shown in Table V.

All patients were maintained on gluten-free diet. The mean weight on follow-up was 18.3 kg (9.3-36) and the mean height on follow-up was 107 cm (77-141).

Repeat small bowel biopsies showed normal villi in 6 patients and partial or subtotal villous atrophy in another 6. Anti-reticulin IgG was positive in 2 patients on follow-up, anti-endomyoseal IgA and IgG were positive in 2 patients, anti-gliadin Ig and IgA were positive in 5 patients.

Table 4. Hemato-biochemical findings

Hematological and Biochemical findings at the time of presentation	Mean Value
Hemoglobin	10.25 g/L (1.72)
Iron	0.23 i g/dL (0.03)
TIBC	3.2 i g/dL (1.91)
Serum ferritin	2.49 ng/mL (3.97)
Serum folate	0.25 ng/mL (1.16)
RBC folate	1.5 ng/mL (0.57)
Vitamin B_{12}	2.2 pg/mL (0.11)
Ca	8.86 mg/dL (0.22)
Alkaline phosphatase	311.5 U/L (231.42)
Serum protein	6.4 g/dL ± (0.99)
Albumin	3.7 g/dL (0.69)
Glucose (Random)	137.5 mg/dL (80)
Na	138 meq/L ± (3.9)
K	4.2 meq/L ± (0.56)
Mg	0.67 mg/dL ± (0.12)

Table 5. Serum Immunoglobulin + Antibodies

Serum Immunoglobulin and other antibodies on presentation		Mean
Ig G		1.26 mg/dL (0.65)
Ig A		0.29 mg/dL(0.10)
Ig M		0.98 mg/dL (0.06)
Ig E		23.31 mg/dL (33)
Anti Reticulin Ig G	1 in	246.5
Anti Endomyceal Ig G	1 in	332.05
Anti Endomyceal Ig A	1 in	720.0
Anti Gliadin Ig G	1 in	121.11
Anti Gliadin Ig A	1 in	300.5

Discussion

The true prevalence of celiac disease in Saudi Arabia cannot be estimated from this small hospital-based study. In all our patients, the diagnostic criteria were met; all patients demonstrated severe histological changes in the jejunal mucosa on biopsy. They showed clinical improvement on exclusion of gluten from the diet. The response to treatment was dramatic, particularly with regard to weight gain. This is in agreement with the findings of Bosio L et al.[7] The prevalence of celiac disease in the female sex appears to be greater than in the male sex. In this series, 22 children were male (36%) and 40 (66.6%) were female. Celiac disease occurs in families, and is found in 5-10% of asymptomatic family relatives; in this study three families had positive consanguinity with more than one affected child. The mean age at presentation of our patients was 4.7 years (range 0.6 -15 years). Unlike in our study, George et al[8] observed 3 years as the mean age of presentation in the Netherlands. The mean age of introduction to cereals in all our patients was 6 months, which is the standard age of introduction to cereals elsewhere in the world as well. Most of our patients presented with failure to thrive (86.2%), chronic diarrhoea (72.4%) and abdominal distention (62%). This is similar to reports from Europe and other countries from the Middle East like Sudan and Kuwait.

CD may present as anaemia, which is secondary to either iron or folate deficiency (10%).[9] The mean serum iron and folate level in our patients were 4.1 mmol/L and 58 nmol/L, respectively. Short stature may be the only presentation of celiac disease, and has been reported by Bottaro et al[2] in 29.9% of his patients with celiac disease. Seventeen (27.4%) of our patients presented with short stature. The pathogenesis of short stature as the only symptom in children with celiac disease is not known but nutritional deficiencies can result in growth failure associated with changes in hormone status.[11]

Another clinical presentation of celiac disease, found in 6 (9.5%) of our patients was rickets. Rickets may be secondary to calcium and vitamin D deficiency, which results from simple intestinal malabsorption, or may be due to interaction between cytokines and local systemic factors influencing bone formation and reabsorption. Mora et al[11] observed low bone mineral content, bone area and bone density in 14 adolescents with celiac disease; there was complete recovery of bone density after 1 year of gluten-free diet and maintenance of normal bone mineral density with prolonged treatment.

Occasionally celiac disease is associated with autoimmune disorders like diabetes and hypothyroidism.[12] These two disorders were found in 19% and 6.3% of our patients.

A recent report from Cataldo et al[13] suggested that an increased prevalence of autoimmune disorders might also be seen in first-degree relatives of CD patients. The strong association with autoimmune thyroid disease is confirmed by the study of Larizza et al[12] who found a 7.8% prevalence of associated autoimmune thyroiditis or Grave's disease in children with CD.

The average prevalence of CD in children with type 1 diabetes mellitus in 26 reports is 4.5% (0.97%-16.4%).[14] The association between CD and type 1 diabetes reported in children living in North America is similar to that reported in Europe;[15] it was 4.3% in a multicentre study in the United States.[16]

Two of our patients had asthma, Battaro et al[2] observed the same in 0.8% of his celiac disease patients.

Another disease associated with celiac disease is epilepsy with occipital calcifications; Labate et al[17] found an increased prevalence of celiac disease in children with occipital partial epilepsy with no brain calcifications. None of the patients suffered from epilepsy. Another mental disorder looked for in association with celiac disease in this study was autism.

Down's syndrome has also been observed in association with CD, and there was one case in our study as well. In a multicentre Italian study on 1,202 patients with Down's syndrome,[18] 55 CD cases were found, with a 4.6% prevalence of disease association.

The serum immunoglobulin scores were normal in all patients, and none of our patients were IgA deficient. Anti-gliadin IgG and IgA were positive in 33 and 34, patients respectively, IgG anti-gliadin antibody was shown to be 89% sensitive and 96% specific by Bürgin-Wolff et al.[18] Anti-endomyseal IgG and IgA were positive in 29 patients. Bonamico et al[19] demonstrated 95% sensitivity and 98% specificity of anti-endomyseal IgA, while Kolho et al[20] showed 95% sensitivity and 100% specificity.

Anti-reticulin antibodies were positive in 19 patients. Another screening test, not performed in this study, for patients with celiac disease, is anti-tissue transglutaminase.

The institution of gluten-free diet should result in dramatic improvement in patient symptoms. Most of our patient improved on gluten-free diet while 15 patients were non-compliant and thus continued to suffer.

Lack of response to the diet may indicate failure to adhere strictly to the diet, sensitivity to other dietary proteins, lymphoma or immune deficiency.

In summary, celiac disease is not common in Saudi Arabia and is still not a major cause of diarrhoea. Careful clinical diagnosis and follow up of all patients with chronic diarrhoea and failure to thrive is highly recommended by testing for either anti-endomyseal antibodies or anti-tissue transglutaminase. Paediatricians should be able to differentiate the clinical picture of celiac disease from internal infections or other causes of chronic diarrhoea, in order to manage this disease early, which responds dramatically to dietary management alone.

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