Coeliac disease in Sudanese children with clinical features suggestive of the disease

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الداء البُطاني لدى الأطفال السودانيِّين الذين تبدو عليهم ملامح سريرية (إكلينيكية) توحي بالمرض

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الخلاصة: تتناول هذه الدراسة الاستباقية المستشفَوِيَّة المرتكَز، تَوَاتُر وقوع الداء البُطاني celiac وتجلياته السريرية (الإكلينيكية) ومؤشِّراته السيرولوجية التي كانت مترابطة مع نتائج الخزعات المعوية لدى أطفال سودانيِّين مرتفعي الاختطار. وقد بيَّنت الدراسة في 80 طفلاً تتراوح أعمارهم بين 15 شهراً و18 عاماً في الفترة ما بين تموز/يوليو 2001 وتموز/يوليو 2002 أنهم كانوا يعانون من نقص الشهية وفقدان الوزن والشحوب وهزال العضلات الدانية. وقد شخص الباحثون الداء البُطاني لدى 18 طفلاً (22.5٪). وكانت أضداد الغليادين (من الغلوبولينات المناعية A أو G أو من كليهما معاً) مرتفعة لدى 44 طفلاً، كما كانت نتائج إعادة اختبار أضداد غمد الليف العضلي مرتفعة لدى 30 طفلاً. وقد رفض أولياء 12 طفلاً الموافقة على إجراء الخزعات، في حين أجريت الخزعات لدى 18 طفلاً، حيث تبيَّن لدى 5 منهم وجود ضمور كامل في الزغابات، ولدى 8 منهم وجود ضمور غير كامل ولدى 5 منهم وجود ضمور جزئي في الزغابات. وقد تحسنوا جميعاً بنظام غذائي يخلو من الغلوتين، و لم تتعلق درجة ضمور الزغابات بمدة الإسهال أو بشدته أو بشدة فقر الدم أو بالعيارات السيرولوجية.

ABSTRACT Our prospective hospital-based study examined frequency, clinical presentation and serological indicators of coeliac disease that correlated with intestinal biopsy among high-risk Sudanese children. From July 2001 to July 2002, 80 children aged 15 months–18 years presented with poor appetite, weight loss, pallor and proximal muscle wasting. We diagnosed coeliac disease in 18 (22.5%). Antigliadin antibodies (AGA-IgG, AGA-IgA or both) were high in 44; endomysial antibody retest was high in 30. Guardians of 12 children refused consent for biopsy. The other 18 were biopsied: 5 had total villous atrophy, 8 subtotal and 5 partial. All improved with gluten-free diet. Degree of villous atrophy did not correlate with diarrhoea duration or severity, anaemia severity or serological titres.

La maladie cœliaque chez des enfants soudanais présentant des signes cliniques évocateurs de la maladie

RÉSUMÉ Notre étude hospitalière prospective a examiné la fréquence, le tableau clinique et les indicateurs sérologiques de la maladie cœliaque qui sont en corrélation avec la biopsie intestinale chez des enfants soudanais à haut risque. De juillet 2001 à juillet 2002, 80 enfants âgés de 15 mois à 18 ans ont consulté pour manque d'appétit, perte de poids, pâleur et amyotrophie proximale. Nous avons diagnostiqué une maladie cœliaque chez 18 enfants (22,5 %). Les anticorps anti-gliadines (AAG-IgG, AAG-IgA ou les deux) étaient élevés chez 44 enfants ; les anticorps anti-endomysium recherchés par le test de confirmation étaient élevés chez 30 enfants. Les tuteurs de 12 enfants ont refusé de donner leur consentement pour la biopsie. Les 18 autres enfants ont subi une biopsie : 5 avaient une atrophie villositaire totale, 8 subtotale et 5 partielle. Tous ont connu une amélioration avec un régime sans gluten. Il n'y avait pas de corrélation entre le degré d'atrophie villositaire et la durée ou la gravité de la diarrhée, la sévérité de l'anémie ou les titres sérologiques.

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Introduction

Coeliac disease has been thought to affect people of European ancestry more often than other ethnic groups [*1*]. Recent studies, however, have revealed increasing global prevalence [*2*].

The disease was first reported in Sudan in 1978 when 7 children were diagnosed [*3*]. Since then, many adult and paediatric cases have also been reported. The disease may in fact be under-diagnosed because of more prevalent conditions such as malnutrition, diarrhoeal diseases and intestinal parasitic infections.

In Sudan diagnosis of coeliac disease has depended upon histological changes of the small bowel biopsy and improvement after withdrawal of gluten from the diet. Serological tests, although non-invasive and reliable, are not yet used routinely [*4*].

Our study aimed to determine the incidence of coeliac disease in Sudanese children who presented with clinical features suggestive of the disease by using serological tests as the initial screening tools. Our study also aimed to identify the sociodemographic and clinical presentation of children with the disease and to correlate serological titres and degree of villous atrophy.

Methods

Our prospective hospital-based study ran from July 2001 to July 2002 in the main paediatric hospitals in Khartoum State (Khartoum Children's Emergency Hospital, Omdurman Children's Emergency Hospital, Ahmed Gasim Teaching Hospital and Khartoum North Teaching Hospital). The study population included 80 children aged 15 months to 18 years who presented with 2 or more of the following: chronic diarrhoea, growth retardation, unexplained iron or folate deficiency anaemia or family history of coeliac disease. Children were excluded if they had systemic illnesses or bloody diarrhoea; were on steroids or on gluten-free diets; or had social and nutritional histories and clinical examinations suggestive of primary protein–energy malnutrition. Verbal consent was obtained from the parents or caregivers.

The data were collected with a predesigned questionnaire. Socioeconomic status was determined by assessing income, literacy, number of family members and lifestyle conditions such as refrigerator and television ownership or internet use.

Each child had a complete clinical assessment with emphasis on anthropometric measurements, signs of nutritional deficiencies and signs suggestive of coeliac disease, such as proximal muscle wasting, abdominal distension, aphthous ulcers or skin lesions of dermatitis herpetiformis. Each child had a complete blood count, total serum protein, serum albumin and stool examination for ova and parasites.

Serological tests, or antigliadin antibodies (AGA) tests, i.e. both AGA-IgA and AGA-IgG, were done for all 80 children using enzyme-linked immunosorbent assay technique (ELISA, binding site MK 035, MK 036) [*5*]. Those with positive AGA tests were retested for endomysial antibodies (EMA) with the indirect immunofluorescence technique; monkey oesophagus was used as a substrate (binding site FK 208) [*6*].

An upper gastrointestinal endoscopy was performed for those with positive AGA and EMA. A second portion duodenal biopsy was taken and the biopsy specimens were fixed in formalin and stained with haematoxylin and eosin. Histological changes specific of coeliac disease were graded as per Levi et al. [*7*]: partial villous atrophy was defined as mild change, subtotal villous atrophy was moderate change and total villous atrophy was severe change with flat mucosa.

Data were analysed with *SPSS*, version 10. Chi-squared test was used to determine 95% significance level.

We diagnosed coeliac disease if a child had 2 or more positive serological markers with biopsy-verified coeliac disease and showed clinical improvement when following a gluten-free diet as per the revised criteria for diagnosis of coeliac disease [*8*]. Haematinics and vitamins were given as needed.

Results

Diagnosis

The study included 80 children (46 boys and 34 girls), of whom 25 (31.3%) had high titres of both AGA-IgA and AGA-IgG. EMA retest was high for 24 of those 25 (96.0%). The parents or caretakers of 11 of these 24 children were among the 12 guardians who refused consent for biopsy. Of the 13 children from this group who underwent biopsy, 4 had total, 6 subtotal and 3 partial villous atrophy.

Three (3.8%) in the study sample had high titre of AGA-IgA, but normal AGA-IgG. EMA titre was high for 2 of these children (66.7%): 1 refused endoscopy and the other had subtotal villous atrophy.

Sixteen children (20.0%) had positive AGA-IgG, but negative AGA-IgA test. EMA titre was high for 4 (25.0%): 1 had total villous atrophy, 1 had subtotal villous atrophy and the remaining 2 had partial villous atrophy.

Thirty-six of the study population (45.0%) were not diagnosed with coeliac disease because they had normal AGA-IgA and AGA-IgG titres.

Twenty-six (32.5%) of the study population probably had the disease but were not confirmed by biopsy. Twelve (46.1%) had high titre of at least 2 serological markers but their caretakers refused to give consent for the biopsy. Five of the 12 responded to gluten-free diet, 1 improved spontaneously after 4 months, and the remaining 6 did not come for follow-up.

Fourteen children had only AGA-IgG positive with negative AGA-IgA and EMA tests, so they were either not coeliac or had coeliac disease associated with IgA deficiency. Two of these followed gluten-free diets, but neither showed improvement. The remaining 12 were not available for follow-up.

Eighteen (22.5%) of the study population had positive AGA and EMA test positives and confirmatory biopsies. When they were put on a restricted gluten-free diet all showed satisfactory clinical improvement; thus, they were confirmed as cases of coeliac disease.

Sociodemographic characteristics

No coeliac child presented during infancy. Of the children diagnosed with the disease, 7 (38.9%) were aged 1–4 years, 5 (27.8%) were aged 5–9 years, 2 (11.1%) were aged 10–14 years and 4 (22.2%) were aged 15 years or older. The mean age at onset of symptoms was 6 years and the mean age at diagnosis was 10 years. The female to male ratio was 1.3:1.

Of the children with the disease, 15 (83.4%) were from north and central Sudan and mainly of Arab ethnic groups, 2 (11.1%) had Egyptian and Turkish ancestry, and only 1 (5.6%) was from southern Sudan from a tribe of pure African ethnicity. Most with the disease were of moderate socioeconomic class (n = 11 or 61.1%), 6 (33.3%) were of low socioeconomic class, and only 1 child was of high socioeconomic class. Among the parents, 9 couples (50%) were first-degree cousins, 4 were second-degree cousins (22.2%) and 5 (27.8%) were not related. There was a family history of coeliac disease for 4 children.

Clinical features

Nine (50%) children who were diagnosed with the disease presented with chronic diarrhoea that was persistent for 6 of the children and intermittent for 3. The frequency was 3–6 motions/day for 6 children and more than 6 motions/day for 3 children. The parents of 3 children described the stool as bulky, pale and offensive. Other significant symptoms were poor appetite (n = 14, 77.8%), abdominal distension (n = 12, 66.7%), vomiting (n = 11, 61.1%) and abdominal pain (n = 7, 38.9%). Pallor was the most common clinical observation (n = 16 patients, 88.9%); 13 children exhibited signs of iron deficiency anaemia. Proximal muscle wasting, abdominal distension and signs of vitamin B_2 (riboflavin) deficiency were common.

Fourteen (77.8%) cases had weight lower than the third centile for age, and 11 (61.1%) had height lower than the third centile for age. Weight-for-height was lower than the third centile for 10 (55.6%). Mid upper arm circumference was less than 12.5 cm for 5 of the 7 coeliac children aged 1–4 years. Six (33.3%) coeliac children had head circumference lower than the third centile for age.

Investigations

One (5.6%) coeliac child had haemoglobin (Hb) less than 5 g/dL and 9 (50.0%) had Hb at 5–9 g/dL. The commonest type of anaemia was iron deficiency (n = 11, 61.1%), followed by combined deficiency anaemia (n = 6, 33.3%); only 1 patient (5.6%) had folate deficiency anaemia. Serum albumin level was low for 5 children with the disease (27.8%). Stool examination for ova and parasites was negative for all 18 children with the disease.

Degree of villous atrophy

Table 1 shows that 6 children had diarrhoea for less than 5 years. Of these, 4 had partial villous atrophy and 2 had subtotal villous atrophy. Three patients had duration of more than 5 years even though 3 had subtotal villous atrophy. This distribution was of no statistical significance (P-value = 0.53).

Table 1 also shows that 1 patient who presented with diarrhoea of more than 6 motions/day had partial villous atrophy. Of those who had subtotal atrophy, 3 had diarrhoea with 3–6 motions/day and 2 had severe diarrhoea with more than 6 motions/day. It is worth noting that all 5 children who displayed total villous atrophy presented without diarrhoea, although this correlation was not significant statistically (P-value = 0.8).

Table 2 shows that 2 of the 5 cases with partial villous atrophy had Hb levels below 9 g/dL, 4 of those who had subtotal villous atrophy had Hb levels at 9–12 g/dL and the

Table 1 Duration and severity of diarrhoea by degree of villous atrophy of 18 coeliac cases

Degree of villous atrophy	Duration (years)						Severity (motions/day)			Total
	No diarrhoea	< 0.5	0.5–2	2–5	5–10	> 10	No diarrhoea	3–6	> 6	
Partial	1	2	2	0	0	0	1	3	1	5
Subtotal	3	0	2	0	1	2	3	3	2	8
Total	5	0	0	0	0	0	5	0	0	5
		Yates corrected $\chi^2 = 0.39$					Yates corrected $\chi^2 = 0.06$			
		P-value = 0.53					P-value = 0.8			

1 child whose anaemia was severe (Hb < 5 g/dL) had subtotal villous atrophy. This correlation was not significant statistically (*P*-value = 0.76).

Villous atrophy and serological titre

Table 3 shows that serological titres for AGA-IgA, AGA-IgG and EMA tests were graded into normal, moderately high, high and very high titre and, when correlated with the degree of villous atrophy (partial, subtotal and total), were not statistically significant (*P*-values = 0.29, 0.35 and 0.54 respectively).

Discussion

Our study was the first in Sudan in which serological tests were used as a screening tool to diagnose coeliac disease. We diagnosed the disease with a high frequency (22.5%) in our high-risk group. Our frequency was higher than in a similar study of Indian children (16.6%) or than among children from north-eastern Libyan Arab Jamarihiya (31.7%) [*9,10*]. In a large sample of unselected Saharan children in western Algeria, the prevalence of EMA positivity was 5.6% [*11*]. The average annual incidence in Kuwait among children was 1:3000 live births and among Jordanian children, 1:2800 live births [*12,13*]. The prevalence of coeliac disease in Israel in the general population was 1:157 [*14*]. In Saudi Arabia, 10 of 48 children (21.0%) who presented with chronic diarrhoea over a 5-year period were diagnosed as coeliac patients [*15*]. The high frequency in our study could be attributed to the genetic background of the Sudanese population, which is a mixture of different ethnic groups, but is primarily Arab and African. Also, Sudanese nutritional habits have changed as cereal-containing meals are now offered early in infancy. Consumption of wheat foodstuffs was not, however, a risk factor for coeliac disease occurrence in Burkina Faso [*16*].

The 4-year delay in diagnosis of the disease in our study might have resulted from the distracting influence of more prevalent conditions in the country that clinically resemble coeliac disease, a lack of awareness of doctors about the occurrence of the disease in Sudan, and the unavailability of serological screening tests.

Coeliac disease affects females more often than males in ratios ranging from 1.3–3:1 [*10,11*]. In our study the ratio was 1.3:1.

Our study partially supports the hypothesis that the disease affects people of middle and high socioeconomic classes more than those of low social class [*17*]. In our study 61.1% of patients were of moderate socioeconomic status and 33.3% of low socioeconomic status, but only 5.6% were of high socioeconomic class. Sudan is

Table 2 Severity of anaemia by degree of villous atrophy of 18 coeliac cases

Degree of villous atrophy	Severity of anaemia				Total
	< 5 g/dL	5–9 g/dL	9–12 g/dL	> 12 g/dL	
Partial villous atrophy	0	2	2	1	5
Subtotal villous atrophy	1	3	4	0	8
Total villous atrophy	1	4	1	0	5
Total	1	9	7	1	18

Yates corrected $\chi^2 = 0.09$; P-value = 0.76.

Table 3 Antigliadin-IgA, antigliadin-IgG and endomysial antibodies titre in relation to degree of villous atrophy in 18 coeliac cases

Degree of villous atrophy	AGA-IgA titre				AGA-IgG titre				EMA titre			Total
	Normal	Moderate	High	Very high	Normal	Moderate	High	Very high	Normal	Moderate	High	Very high	
Partial	2	2	1	0	0	3	2	0	0	3	2	0	5
Subtotal	1	3	3	1	1	1	6	0	0	4	3	1	8
Total	1	0	3	1	0	1	3	1	0	0	4	1	5
	Yates corrected $\chi^2 = 1.11$ P-value = 0.29				Yates corrected $\chi^2 = 0.87$ P-value = 0.35				Yates corrected $\chi^2 = 0.36$ P-value = 0.54				

a developing country in which the low and the middle classes are more prevalent than the higher social class.

Nine coeliac children presented with chronic diarrhoea, i.e. classic presentation, whereas the other 9 had atypical presentation. It has been reported that 50% of newly diagnosed patients have no gastrointestinal problems [*18*].

Signs of vitamin A deficiency and skin lesions of dermatitis herpetiformis were not observed for any child. This could have been due to our small sample size.

In our study, 1 child with type 1 diabetes mellitus was diagnosed with coeliac disease. The association between type 1 diabetes mellitus and coeliac disease has been well established [*19*]. We also diagnosed a child who had features of Down syndrome with probable coeliac disease but for whom biopsy was refused; this association has also been well documented [*20*]. We diagnosed identical twin boys with probable coeliac disease and they showed remarkable improvement with a gluten-free diet. The concordance rate for identical twins is 70%–100% [*18,21*]. An 8-year-old boy presented with signs of myopathy in addition to his coeliac-like condition. He was diagnosed with probable coeliac disease and improved after gluten-free diet. This was similar to a report of a case of coeliac disease associated with rickets and myopathy that was attributed to calcium and vitamin D malabsorption [*22*].

Hb levels ranged from 5 to 12 g/dL in 16 patients and only 1 child had severe anaemia. Severe anaemia is rather uncommon in coeliac disease and should raise the suspicion of a malignant complication [*1*].

Low albumin levels indicated a severe form of the disease for 5 coeliac patients [*18*].

AGA-IgG is very sensitive but less specific and AGA-IgA is less sensitive but

more specific. Their use in combination results in a high detection rate [*23*]. This was borne out by our study as 16 children were IgG positive and IgA negative; when EMA was retested, it was positive for only 4 (25.0%) of them. Furthermore, 25 children had both positive AGA-IgA and AGA-IgG and EMA retest was positive for 24 (96.0%) of them. 28 children had positive AGA-IgA, either alone or in combination with positive AGA-IgG, and 26 (92.8%) of them had positive EMA test. Three children had positive AGA-IgA and negative AGA-IgG; 2 (66.6%) of them had positive EMA tests.

EMA test has been the single most predictive test for coeliac disease [*6,24,25*]. We found that all children with positive EMA test displayed mucosal changes characteristic of the disease.

We expected that duration and severity of diarrhoea and severity of anaemia would correlate with degree of villous atrophy and that serological titres would correlate with degree of villous atrophy. We found no correlation, but these discrepancies could be attributed to our small sample size.

Conclusions

We confirmed that coeliac disease is a cause of malabsorption in Sudanese children. Its frequency in a selected high-risk group was 22.5%. Females were affected more often than males with a ratio 1.3:1. Ages between onset of symptoms and diagnosis were delayed. Children from Arabic tribes and from middle socioeconomic class were affected more often than others. Coeliac children presented with or without frank gastrointestinal symptoms. Pallor and severe weight loss were the predominant signs. The commonest type of anaemia was iron deficiency.

AGA-IgG was very sensitive but less specific, AGA-IgA was less sensitive but more specific, and EMA test was highly specific.

Our study revealed no correlation between severity, duration of diarrhoea and severity of anaemia with degree of villous atrophy. There was no correlation between the serological titres and the degree of villous atrophy.

The majority of parents in our study were apprehensive about intestinal biopsy and many refused permission to perform the procedure.

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