Some Diagnostic Aspects of Celiac Disease in Iraqi children.

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Abstract

Background: There has been an increasing appreciation of the high prevalence of celiac diseas around the world and efforts are continuing to clarify the variable diagnostic problems of the disease.

Objective: We tried to throw light over some of these problems in a group of Iraqi children.

Methods: Ninety-three patients with features of malabsorption were evaluated for celiac diseas, by assessing serum IgA tTG, both IgG & IgA AGA, serum IgA level and a small intestinal biopsy.

Results: Fifty-eight out of ninety-three patients proved to have celiac diseas according to the histopathological picture. Sensitivity of serological tests in general ranged between 50- 77%, but tTG was 100% specific. Patients with more severe histopathological changes showed more serological positivity and higher antibody titers.

Eleven cases of Giardiasis were diagnosed (on biopsy specimen) out of the whole sample, giving variable histopathological changes & serological responses.

Conclusion: celiac diseas is a prevalent problem in Iraqi children. We share with other countries the diagnostic problems of the disease, but there seems to be some additional aspects, that are peculiar to developing countries, implying the need for diagnostic strategies specific to these areas.

Key words: celiac disease, serological tests, histopathology

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Introduction

Celiac disease (CD) is a problem prevalent around the world. It's prevalence has been increasingly appreciated recently, studies primarily in Europe, but also in the United States, now suggest that it's prevalence is roughly 1%, among the general population[(1)]. This better appreciation occurred with the advent of newer diagnostic techniques (including the easy-to-administer serology tests), that clarified many of the non-specificity of the diagnostic techniques [(2)].

Has been frequently rejected by families as being unduly invasive, especially when evaluating problems as anemia, short stature or even chronic diarrhea in their children.

Reports of CD in Iraq first appeared in 1975 by Al-Hassany [(3)], relying on having a proper small intestinal biopsy showing characteristic histology. However, in Iraq as in other developing countries, the facility for obtaining a biopsy is not always available; in addition, this invasive procedure

On the other hand, children in developing countries are prone to multiple disease states that may lead to clinical manifestations mimicking CD, and even to proximal small intestinal mucosal lesions like: tropical sprue, persistent infection or infestation, post infectious complications or protein energy malnutrition [(5, 6)]. A situation which is pressing to provide better diagnostic tools, to avoid misinterpretation of test results and if at all possible to

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spare the child from costly, invasive techniques.

Patients & Methods

A total of 93 consecutive cases, with malabsorption, presenting with different complaints: chronic diarrhea, chronic abdominal pain, abdominal bloating, anemia, growth retardation….etc, were evaluated for having celiac disease. Their ages ranged from 1- 18years. All those patients were referred to the Iraqi center for gastrointestinal diseases in Baghdad, during the period from Sept. 2001-Apr 2002. After fulfilling the routine initial clinical and Lab evaluation, they have undergone an endoscopic small intestinal biopsy and serological evaluation for celiac disease.

Biopsies were interpreted histopathologically according to the gluten-sensitivity spectrum described as follows [7]: Marsh 0: normal, Marsh I: there is intraepithelial lymphocytes (IELs), Marsh II: IELs+ hyperplasia of crypts, Marsh III: influx of inflammatory cells, hyperplasia of crypts and villous atrophy, III A: partial villous atrophy (PVA)-(villous / crypt ratio< 1:1)

III B: subtotal villous atrophy (SVA), villi are clearly atrophic, but separated villi are still recognizable.

III C: total villous atrophy (TVA), villi are rudimentary or absent.

Diagnosis of CD was only been made by demonstration of Marsh III lesion in small intestinal biopsy [7].

Serological testing included:

- Enzyme immunoassay kit for detection of human anti-tissue transglutaminase IgA in serum (Biohit-Finland)

Values <10 AU (arbitrary unit) were regarded –ve, 10-15 weak +ve, >15 +ve.

- Enzyme immunoassay kits for detection of both Anti-gliadin IgG and IgA antibodies in serum (Biohit-Finland)

In<2yr of age: a titer <50 regarded as –ve, 50-100 weak +ve, >100 +ve

- Single radial immunodiffusion test (SAIDT) plates (Sanofi Diagnostic Pasteur, Inc-USA): for measurement of total IgA level in serum.

Analysis between different variables was done using Chi-square test and student T-test. The level of significance was considered when P-value <0.05.

Results

A total of 93 patients with different complaints suggestive of malabsorption were evaluated for the diagnosis of CD (51 males), their ages ranged from 1 yr- 18 yrs. Fifty eight were diagnosed as having celiac disease according to histopathological picture (28 males, male/female ratio:0.93), their ages ranged from 18 mo- 18yrs, with a mean of 9.5yrs.

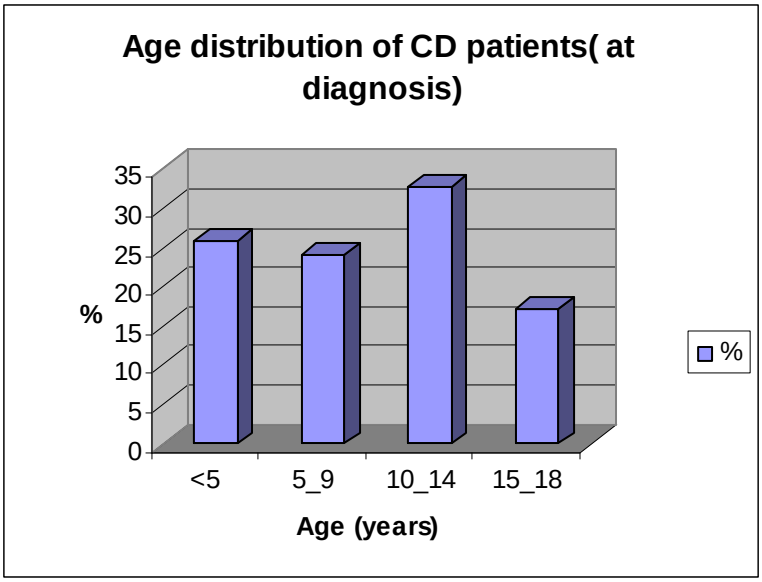

Figure 1: shows that the disease was diagnosed mostly in the age group 10-14 yrs, next to it those < 5yr of age.

The diagnosis relied on histopathological findings (the presence of Marsh III changes), from table (1), it can be calculated that 50% of the patients were having severe HP changes, Marsh III C (total villous atrophy TVA), and especially for the older aged patients (>10yr), in whom TVA was seen in 80% of them.

Table 1: Correlation between age & histopathological severity of CD patients

Age(years)	HP stage						Total	
	Marsh A		Marsh B		Marsh C			
	No.	%	No.	%	No.	%	No.	%
<5	5	33.3%	4	26.6%	6	**40%**	15	100
5-9	3	21.4%	5	35.7%	6	**42.8%**	14	100
10-14	6	31.5%	4	21%	9	**47.4%**	19	100
15-18	2	20%	0	0	8	**80%**	10	100

Table (2) , shows that tTG assay gave moderate sensitivity and perfect (100%) specificity, while the antigliadine antibodies (igG and IgA) being both less specific, the IgG type was somewhat more sensitive.

Table 2: Serological markers in celiac patients & controls

Patients	Total	tTG		IgA AGA		IgG AGA	
		+ve	-ve	+ve	-ve	+ve	-ve
Celiac	58	35	23	29	29	45	13
Non Celiac	35	0	35	5	30	5	30
Sensitivity		60.3%		50%		77.6%	
Specificity		100%		85.7%		85.7%	

In patients with severe histopathological changes (total villous atrophy or Marsh IIIC) about 90% of them were seropositive (~90%) for tTG, and such patients showed much higher titers than others with milder histological changes, the difference was statistically significant. The same picture was shown with the antigliadin antibodies, table (3)

Table 3: Serological titers against severity of histopathological changes

Marsh III	No.	tTG+ve	tTG titer			
		No.	%	Mean±SD	Median	
A	16	6	37.5	9.69±10.54	4	P value: 0.000289 (significant)
B	13	3	23.1	7.31±11.39	3	
C	29	26	**89.7**	24.03±14.44	**25**	
Marsh III	No.	IgA AGA+ve	IgA AGA titer			
		No.	%	Mean±SD	Median	
A	16	5	31.3	40.5±56.18	14.5	P value: 0.00045 (significant)
B	13	2	15.4	17.23±34.68	0	
C	29	22	**75.9**	75.45±75.16	**68**	
Marsh III	No.	IgG AGA +ve	IgG AGA titer			
		No.	%	Mean±SD	Median	
A	16	12	75	60.56±61.55	41.5	P value: 0.00246 (significant)
B	13	7	53.8	32.69±63.08	30	
C	29	26	**89.7**	100.35±61.93	**98**	

Giardiasis was diagnosed in 11 (out of the 93 studied cases), by demonstrating the parasite attached to the mucosal surface of the biopsy, three of these patients showed histological changes (Marsh III A or

B), two of them with +ve IgG AGA, the third one was seronegative for all the 3 serological markers but was at the same time deficient in the total IgA, one patient reacted positively to the IgG antigliadin only with normal histology and was dismissed as Giardiasis. The remaining 7 cases of giardiasis were seronegative to all tests with normal s.IgA level. whether these results were due to Giardiasis or a concomitant celiac disease?, anyhow the 3 patients were put on gluten free diet (GFD) in addition to antiGiardia therapy, but unfortunately long-term follow up was not possible for these patients.

Table 4: Cases of Giardiasis

Marsh score		AGA		tTG	IgA
		IgG	IgA		
1	0	-ve	-ve	-ve	Normal
2	III B	-ve	-ve	-ve	***Deficient***
3	0	-ve	-ve	-ve	Normal
4	0	+ve	-ve	-ve	Normal
5	III A	+ve	-ve	-ve	Normal
6	III B	+ve	-ve	-ve	Normal
7	0	-ve	-ve	-ve	Normal
8	0	-ve	-ve	-ve	Normal
9	0	-ve	-ve	-ve	Normal
10	0	-ve	-ve	-ve	Normal
11	0	-ve	-ve	-ve	Normal

Discussion

People until recently thought that the geographical distribution of celiac disease was mostly restricted to Europe and other developed countries, nowadays in part due to the availability of the simple serological diagnostic tests, globalization of the problem of Celiac disease is ensured, following the recognition of increasing reports of the various forms of the disease from developing countries [8,9].

Celiac disease formed a significant part of our patients evaluated for malabsorption (about 62%). In an Indian study by Behera etal [10], CD formed 72% of causes of malabsorption in children and 52% of those in adults, pointing to the higher propensity of CD as a cause of malabsorption in developing countries.

About half of our CD patients were older than 10 years,with a similar age incidence also documented by a previous Iraqi study. (Mohammed et al, 2001)[11], whether this was due to delayed diagnosis of the problem in our pediatric population, or probably mimicking the changing picture of CD reported by several researchers [12,13] in which the median age at presentation in children has shifted from early to late in the first decade of life. Still, most of our patients showed severe H.P changes (TVA), especially demonstrated in the older aged group, strengthening the probability of delayed diagnosis.

Serological markers showed variable sensitivity rates in our patients, in general ranging between 50% -77%, while tTG seemed to be specific enough to ensure the presence of celiac disease. The combined determination of AGA (IgG & IgA)

and tTG (IgA) gave a better diagnostic ability, especially if there was concordance in the results of the 3 antibodies. The positive predictive value of tTG was 100%, while the negative predictive value of the 3 antibodies was 60.3%, this may offer a good strategy for disease identification with 100% specificity of the 60.3% of untreated CD patients, and for the exclusion of nearly 100% of non-celiac patients from unnecessary biopsy.

The validity of testing for serological markers in our studied group seemed to be comparable with the average international figures(14-18), accept for a lower sensitivity of tTG; our data gave sensitivity 60%, while most researchers agree to a sensitivity around 90-100% even those from developing countries[12,19,20,21]. In general these antibody tests are thought to fare less well in the clinical practice setting than in the research setting [22,23]. Standardization and quality control of these tests is an important issue [24,25], and attempting a national standardization initiative to achieve this goal specifically in developing countries [26,27] due to the some what peculiar state of CD diagnosis there.

Tissue transglutaminase, being simpler to perform than antiendomysial antibodies, with the high concordance between the two, has been repeatedly recommended as the serology of choice in developing countries [19, 28]. According to our results, we may recommend the cumulative outcome of tTG and both Antigliadines giving better prediction of the disease in these areas.

Patients with severe H.P changes, in the studied patients, showed higher positivity of serological markers, 89.7% for tTG, 75% for IgA AGA, and 89.7% for IgG AGA antibodies, in addition those patients gave the highest titers, much above the cutoff value. This same picture has led Barker etal [29] from Canada, and Danaldson et al [30] ,at the University of Utah and the University of California Irvine, in their retrospective analysis to suggest raising the cutoff value of tTG to >100 IU (in patients with normal IgA), finding that about 96-98% of such patients had positive biopsy and proved to have CD, hoping in future to avoid totally the need for biopsy [29], but still this would need further approval by other studies in order to be applied practically, and the time to abandon an intestinal biopsy in the diagnosis of CD seems not to have come yet [2,13,21,31].

Roughly, about 10% of cases of CD are difficult to diagnose because of lack of concordance among serologic, clinical, and histologic findings [19]. Even mild mucosal changes (Marsh I, II), could be a presentation of celiac disease, and in symptomatic patients, provided other diagnostic criteria were included (HLA haplotype …etc), GFD would be indicated [32-35]. While in children in developing countries, mild–moderate mucosal changes are less specific as they could be induced by persistent enteric infection or parasitic infestation…etc, the so-called environmental enteropathy [28,36] rather than CD, still some recent reports are appearing from these countries, that even there, CD might present with variable histological pictures and the diagnosis maybe missed or delayed if based only on severe enteropathy [27].

Behera [India], have shown that patients with malabsorption harbor more pathogenic parasites as compared to healthy controls [8]. Giardiasis was diagnosed by duodenal biopsy in our studied patients in 11 out of 93 cases. All the 11 patients were seronegative for tTG & IgA AGA, 3 of them showed severe mucosal changes (Marsh III), with variable reactions towards only the IgG AGA, whether

this whole picture was inflicted by Giardial infection alone or a coexistent gluten hypersensitivity, unfortunately follow up was not possible to evaluate their response to gluten free diet.

Revision of the diagnostic criterias of Celiac disease (in the form of standardization of serologic tests and pathologic criteria) is persistently called for by workers in this field [1,35], with the need for a special consensus for diagnosis in developing countries.

Celiac disease is a common cause of malabsorption in Iraqi children, presenting a persistent diagnostic challenge to pediatricians and gastroenterologists, with the variable efficacy and availability of serological tests in the country, and the endemicity of parasitic infestations in the pediatric population with the mucosal changes they may induce, adding a challenge for additional efforts to clarify diagnostic criteria of CD, especially in developing countries.

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