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RESEARCH ARTICLE

UTILITY OF SEROLOGICAL TESTS FOR THE CLINICAL DIAGNOSIS OF CELIAC DISEASE IN CHILDREN IN DIYALA PROVINCE

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ABSTRACT

Background: Celiac disease (CD) is an immune-mediated systemic condition triggered by dietary gluten occurring in genetically susceptible individuals. CD has a wide range of clinical manifestations. A number of serologic tests were implemented in the diagnosis of CD.
Objectives: This case-control study was arranged to evaluate the validity of clinical presentations and to assess the clinical utility of serologic tests in the diagnosis of CD in children in Diyala province.
Subjects and Methods: The present study was conducted in Diyala province-Iraq during the period from September 2011 to April 2012 in Al-Batool Teaching Hospital for Maternity and Children. One hundred sixty five children who were clinically suspected as having CD and 124 healthy children as control group were enrolled. The patient's age range was 1 month to 6 years and above. Information regarding age, sex, residence, family history, and clinical signs were collected in a special questionnaire. Commercially available serological kits for anti-gliadin IgA (AGA-IgA) and anti-tissue transglutaminase IgA (anti-tTG-IgA) antibodies (Aeskulisa, Germany) were used by ELISA technique. Data were statistically analyzed, and P value < 0.05 was considered significant.
Results: Based on the seropositivity of both anti-AGA IgA and anti-tTG IgA, 15 (9.6%) were considered CD patients. whereas, patients who had either anti-AGA IgA (16.7%) or anti-tTG IgA (14.7%) positive were considered as symptomatic non-CD patients. The results showed that the anti-AGA IgA and anti-tTG IgA seropositivity was highly significant (P< 0.001) in CD patients compared to symptomatic non-CD patients and control groups. The anti-tTG IgA has higher specificity, accuracy, and positive predictive value. Two or more clinical manifestations together were significantly increase the validity of clinical diagnosis of CD, and correlate well with the results of serological tests.
Conclusion: CD has wide intestinal and extraintestinal clinical manifestations. Accordingly, patients presented with two or more of these clinical manifestations should be serologically screened for CD. The anti-AGA IgA and more specifically the anti-tTG IgA are highly informative for early detection of CD.

INTRODUCTION

Celiac disease is multifaced autoimmune disorder triggered by dietary gluten occurring in genetically susceptible individuals (Evans and Sanders, 2012). Understanding of its numerous and varied clinical presentations has evolved over time (Ma *et al.*, 2013). Therefore, clinical identification of CD is challenging because it can begin not only with diarrhea and weight loss but also with atypical gastrointestinal and extra-intestinal symptoms, or it may be completely symptomless with possible onset at any age and with many possible clinical Presentations (McGough and Cummings, 2005; Mustalahti, 2006; Ravikumara *et al.*, 2006; Volta, and Villanacci, 2011; Paul *et al.*, 2013).

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The clinical manifestations of CD vary markedly with the age of the patient, the duration and the extent of disease (Savilahti *et al.*, 2010; Guarino *et al.*, 2012). Hence, it has been suggested that the current illness-defining criteria should be revised so to implement early diagnosis and improve the patients' quality of life and access to treatment (Angeli *et al.*, 2012). It has been documented that CD is common not only in Europe, but also in the developing countries where the major staple diet is wheat (Southern Asia, the Middle East, North West and East Africa, South America), both in the general population and in the groups at risk. The prevalence of CD in at-risk populations in these regions is reported to range between 3 and 20% and the prevalence in people with type 1 diabetes is approximately 3-5% (Malekzadeh *et al.*, 2005; Cataldo and Montalto, 2007 ; Barada *et al.*, 2010; Al-Hussaini *et al.*, 2012; Ben Hariz *et al.*, 2007). Furthermore, clinical

presentation with non-specific symptoms or no symptoms is as common in the Middle East as in Europe (Rostami *et al.*, 2004; Farahmand *et al.*, 2012; Assiri *et al.*, 2013; Vijgen *et al.*, 2012). Over the last 20 years, the diagnostic accuracy of serology for CD has progressively increased with the implementation of highly sensitive and specific tests, such as the detection of IgA tissue transglutaminase and antiendomysial and IgG antideamidated gliadin peptide antibodies, although it may not always correlates with mucosal appearance in the small intestine (Ludvigsson *et al.*, 2009; Volta *et al.*, 2012; Baudon *et al.*, 2004; Giersiepen *et al.*, 2012). Utilization of such serological markers has discovered a very high number of borderline cases that can be classified as potential CD, possibly through identifying CD in its early stages before the appearance of severe intestinal damage, and that may obviate the need for duodenal biopsy (Leeds *et al.*, 2008; Lurz *et al.*, 2009; Vermeersch *et al.*, 2012). The present study was to evaluate the validity of clinical presentations and to assess the clinical utility of serologic tests in the diagnosis of CD in children in Diyala province.

MATERIALS AND METHODS

This case control study was conducted in Diyala province-Iraq during the period from September 2011 to April 2012 in Al-Batool Teaching Hospital for Maternity and Children. 156 children who were clinically suspected as having CD and 124 apparently healthy children as control group were enrolled. The patient's age range was 1 month to 6 years and above. Sociodemographic data including age, sex, residence, family history, and clinical signs were collected in a special questionnaire. For human privacy, the patient parent's consensus was taken. Commercially available serological kits for anti-gliadin IgA (AGA-IgA) and anti- tissue transglutaminase IgA (anti-tTG-IgA) antibodies (Aeskulisa, Germany) were used by Enzyme-Linked Immunosorbant Assay (ELISA) technique following the manufacturer's instructions. Statistical analysis was done through the computerized software, Statistical Package Social Sciences (SPSS) version 20 by using the Chi-square. P value < 0.05 was considered significant.

RESULTS

Based on the seropositivity of both anti-AGA IgA and anti-tTG IgA, 15 (9.6%) were considered CD patients. whereas, patients who had either anti-AGA IgA (16.7%) or anti-tTG IgA (14.7%) positive were considered as symptomatic non-CD patients (SNCD). The results showed that the anti-AGA IgA seropositivity was highly significant (P< 0.001) in CD patients compared to SNCD patients. Likewise, the anti-tTG IgA positivity was highly significant (P< 0.001) in CD patients

Table 1. The seropositivity rate of serological tests among study groups

Test	SNCD patients No. (%)	CD patients No. (%)	Total No. (%)	P value	95% CI
Anti-AGA IgA					
No	130 (100)	0 (0)	130 (100)	< 0.001	(42.8- 2887.2)
Yes	11 (42.3)	15 (57.7)	26 (100)	[S]	
OR= 351.8					
Anti-tTGIgA					
No	133 (100)	0 (0)	133 (100)	< 0.001	(57.8- 4097.3)
Yes	8 (34.8)	15 (65.2)	23 (100)	[S]	
OR= 486.9					

Table 2. Validity of anti-AGA IgA and anti-tTA IgA

Test	Sensitivity	Specificity	Accuracy	Positive PV		Negative PV
				50%	90%	100%
Anti-AGA IgA	100.0	92.2	92.9	92.8	99.1	100.0
Anti-tTGIgA	100.0	94.3	94.9	94.6	99.4	100.0

Table 3. Association of clinical manifestations with serological tests

Clinical sign	SNCD patients No. (%)	CD patients No. (%)	Total No. (%)	P value	95% CI
Abdominal pain					
No	103 (93.0)	8 (7.0)	115 (100)	0.067	(0.93-8.15]
Yes	34 (82.9)	7 (17.1)	41 (100)	[NS]	
OR= 2.8					
Chronic diarrhea					
No	44 (89.8)	5 (10.2)	49 (100)	0.86	(0.29-2.8)
Yes	97 (90.7)	10 (9.3)	107 (100)	[NS]	
OR= 0.9, IOR= 1.1					
Constipation					
No	132 (89.8)	15 (10.2)	147 (100)	0.46	(0.05-3.75)
Yes	9 (100)	0 (0%)	9 (100)	[NS]	
OR= 0.4, IOR= 2.2					
Glucose intolerance					
No	135 (90.0)	15 (10.0)	150 (100)	0.71	(0.08-5.82)
Yes	6 (100)	0 (0)	6 (100)	[NS]	
OR= 0.7, IOR= 1.5					

compared to SNCD patients, Table (1). Table (2) revealed that the anti-AGA IgA and anti-tTG IgA were equal in their sensitivity, but the anti-tTG IgA test had higher specificity, accuracy, and positive PV. Table (3) revealed the relation among the clinical signs and symptoms with the diagnosis of CD based on serological tests. The abdominal pain was found in 82.9% of SNCD patients and 17.1% of CD patients with an insignificant association (P= 0.067), although the presence of abdominal pain increases the probability of diagnosis by 2.8 times (Odd ratio = 2.8).

Table 4. Association of clinical manifestations with serological tests

Clinical sign	SNCD patients No. (%)	CD patients No. (%)	Total No. (%)	P value	95% CI
bloating					
No	103 (91.2)	10 (8.8)	113 (100)	0.6	(0.44-
Yes	38 (88.4)	5 (11.6)	43 (100)	[NS]	4.22)
OR= 1.4					
Type 1 DM					
No	136 (91.3)	13 (8.7)	149 (100)	0.16	(0.74-
Yes	5 (71.4)	2 (28.6)	7 (100)	[NS]	23.7)
OR= 4.2					
Short stature					
No	133 (90.5)	14 (9.5)	147 (100)	0.87	(0.14-
Yes	8 (88.9)	1 (11.1)	9 (100)	[NS]	10.2)
OR= 1.2					
Delayed mile stone					
No	97 (91.5)	9 (8.5)	106 (100)	0.49	(0.49-
Yes	44 (88)	6 (12)	50 (100)	[NS]	4.38)
OR= 1.5					

Table 5. Association of clinical manifestation groups with the serological tests

Clinical sign	SNCD patients No. (%)	CD patients No. (%)	Total No. (%)	P value	95% CI
1 positive clinical sign	44 (100)	0 (0)	44 (100)	*	*
2 positive clinical signs	81 (88.0)	11 (12.0)	92 (100)	0.017*	(1.5-99.7)
3-4 positive clinical signs	16 (80.0)	4 (20.0)	20 (100)	0.005*	(2.6-223.1)

On the contrary, the presence of constipation decreases the probability of diagnosis by 2.2 times (IOR=2.2, P= 0.46). Similarly, the chronic diarrhea and glucose intolerance had inverse association with the diagnosis of CD (Inverse odd ratio = 1.1 and 1.5 respectively). The results also found that the presence of type 1 diabetes mellitus increases the probability of diagnosis by 4.2 times (OR= 4.2); However, the association was insignificant (P= 0.10). Likewise, the presence of bloating, short stature and delayed mile stone, all increases the probability of diagnosis, even though there was insignificant association with the diagnosis of CD, Table (4). Ultimately, it is clear that the presence of one positive clinical sign does not make any significant difference in the diagnosis of CD. However, the co-presence of two positive clinical signs significantly increase the diagnosis of CD (OR= 12.6, P= 0.017). Similarly the presence of three or four positive clinical signs has significantly increases the probability of diagnosis by 24.3 times (OR= 24.3, P= 0.005), Table (5).

DISCUSSION

There has been growing recognition of a changing clinical presentation of CD, so that most children with CD remain undiagnosed mainly because of lack of awareness of its heterogeneous clinical presentation (Ma *et al.,* 2013; Ravikumara *et al.,* 2006; Lanzini *et al.,* 2005). Basically, and according to CD guidelines; the diagnosis is established by small bowel biopsy. Consequently, a number of serologic tests were introduced for identifying individuals who require an intestinal biopsy examination. Over the last few years, the diagnostic accuracy of serology for CD has progressively increased with the implementation of highly sensitive and specific tests (Volta *et al.,* 2012; Giersiepen *et al.,* 2012). However, the potential dilemmas in CD diagnosis are still including those with positive serology but normal intestinal histology, negative serology but abnormal duodenal mucosal histology. The present study was conducted to address two questions; firstly, what is the clinical utility of serologic tests in the diagnosis of CD? Considering that the clinical utility is the impact of the test on decision making, and secondly what is the validity of clinical signs and symptoms in the diagnosis of CD? Considering that the clinical validity is the ability of the clinical presentation to change diagnosis (Health Quality Ontario, 2010).

Table 6. Hemoglobin concentration among study groups

Hb conc.(gm/dl)	Healthy (n=124)	SNCD (n=141)	CD (n=15)	P value
Range	(9-12.6)	(7.3-14.5)	(6.2-12.8)	
Mean	10.9	10.9	10.5	0.49 [NS]
SD	0.85	1.13	1.56	
SE	0.17	0.09	0.40	

Because the facilities for duodenal biopsy was not feasible in our health care settings, the study was based on the seropositivity of both anti-AGA IgA and anti-tTG IgA, to determine CD patients. whereas, patients who had either anti-AGA IgA or anti-tTG IgA positive were considered as symptomatic non-CD patients (SNCD). The results showed that the anti-AGA IgA and anti-tTG IgA are equal in their sensitivity, but the anti-tTG IgA test had higher specificity, accuracy, and positive PV in the diagnosis of CD. These results are consistent with other workers who documented that these tests were highly correlates with villous atrophy (Mustalahti

2006; Omar 2011), with the superiority of anti-tTG IgA in the diagnosis of symptomatic CD (Volta *et al.,* 2012; Giersiepen *et al.,* 2012; Lurz *et al.,* 2009; Naiyer *et al.,* 2009; Reeves *et al.,* 2006), asymptomatic or occult CD (Farahmand *et al.,* 2012; Omar, 2011), as well as in the monitoring response and compliance with a gluten-free diet (Gillett *et al.,* 2006). The results revealed that none of the clinical signs that are considered in this study; abdominal pain, chronic diarrhea, constipation, glucose intolerance, bloating, short stature or delayed mile stone, individually doesn't make any significant difference in the diagnosis of CD, even the presence of type 1 DM, although it increases the risk factor by 4.2 times. In spite of that, the present study supporting the previous documents that the presence of type 1 DM was the most common indication for regular screening for CD (Al-Hussaini *et al.,* 2012; Omar 2011; Gillett *et al.,* 2006). On the other hand, the co-presence of two or more clinical signs was significantly increases the clinical validity in the diagnosis of CD and significantly correlates with positive serological tests. The most acceptable explanation for that is the wide and heterogeneous clinical presentation of CD (Ravikumara *et al.,* 2006; Volta, and Villanacci, 2011; Paul *et al.,* 2013; Jones and Sleet, 2009). Therefore, the disease is substantially underdiagnosed in the primary health care, where several studies have suggested that as few as quarter of population with CD were recognized, and the disease is much more common than previously believed (Ma *et al.,* 2013; Ravikumara *et al.,* 2006; Tikkakoshi *et al.,* 2007).

In the Middle East, as in other parts of developing countries, the CD is common among both general population and risky groups as documented by several studies (Malekzadeh *et al.,* 2005; Al-Hussaini *et al.,* 2012; Ben Hariz *et al.,* 2007; Hill, 2005; Abu-Zekry *et al.,* 2008). These results can be explained on the fact that wheat has been the major staple food in these regions for a long time and possibly that the continuous and high level of exposure to wheat proteins has induced some degree of immune tolerance, leading to milder symptoms, which are misdiagnosed as irritable bowel syndrome or unexplained gastrointestinal disorders (Omar 2011).

The results also found that the mean hemoglobin concentration was insignificantly differ among CD, SNCD, and healthy groups. Actually, in all these three groups, the Hb concentration is lower than the hemoglobin cut-off value for anemia in children 6 months-14 years old (11-12 gm/dl) (Lother, 1998). However, the prsence of anemia and iron deficiency in CD patients were controversial (McGough and Cummings, 2005; Savilahti *et al.,* 2010; Ludvigsson *et al.,* 2009; Volta *et al.,* 2012; Lurz *et al.,* 2009). The low hemoglobin concentration among children enrolled in the present study may be related to several reasons including; neglegted children health care, inbalanced food meals, unhealthy inherited feeding customs, and poverty. In conclusion, CD in our region has a wide intestinal and extraintestinal clinical manifestations. Accordingly, patients presented with two or more of the following; abdominal pain, chronic diarrhea, bloating, short stature, type 1 DM, and delayed mile stone should be seologically screened for CD. The anti-AGA IgA and more specifically the anti-tTG IgA are higly informative for early detection of CD.

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