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TTG IgA in Functional Constipation: Is It Rational to Be Evaluated?

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Abstract

Background: It is suggested that constipation could be due to celiac disease (CD); therefore, this study aimed to determine the prevalence of positive tissue transglutaminase (tTG) IgA test among children with functional constipation (FC).

Methods: In this case-control study, 182 consecutive patients with FC who fulfilled the Rome III criteria as cases were compared with 240 healthy children as the control group in terms of suspicious CD by measuring the serum tTG IgA level.

Results: There was a significant difference in favor of the case group in terms of serum tTG IgA levels ($P=0.000$). The probability of having CD would change based on belonging to each group (case/control odds ratio [OR] = 0.222).

Conclusion: With respect to these data, tTG IgA level was observed to be significantly higher in patients relative to healthy children; therefore, it is recommended that patients be screened for CD through the tTG IgA.

Keywords: Functional constipation, Celiac, Tissue transglutaminase, IgA.

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Background

Functional constipation (FC) is recognized as a frequent problem in children. Although constipation could be due to organic or anatomical reasons, it is most commonly FC for which there is no obvious organic or anatomical reason.[1-3] The most common initiator of FC in childhood is an experience of painful defecation.[4] The estimated prevalence of FC is between 0.3% to 8% of pediatric population that is different according to race and geographic regions.[2,4] The FC is diagnosed based on Rom III criteria and there is no need for laboratory workup except for precise history and physical examination,[1-5] though some authors suggest evaluation for celiac disease (CD) in constipated patients especially in severe and refractory cases before making the diagnosis of FC in such patients.[5,6] CD is commonly manifested at any age with chronic diarrhea, loose stool, vomiting, abdominal distention, constipation, or symptoms of malabsorption syndrome; however, recently presenting CD as a malabsorption syndrome is not a rule.[8-10] Its symptoms and age of presentation have also changed.[9,10] The important message of these alterations is that panorama of CD may change according to the community. Altered pattern of CD and observation of completely asymptomatic forms of disease reveal the fact that the typical CD represents just the tip of iceberg. Hence, it should be kept in mind that CD might occur with uncommon presentations such as FC.[11-13]

Today, clinicians use the tissue transglutaminase (tTG) IgA for determining CD as highly indicative of CD and according to population-based studies, its positivity is hand to hand with CD specific HLA genes and also correlates strongly with the intestinal mucosal damages.[8,9,14]

With this insight that tTG IgA is trustable screening test and CD may potentially be presented with constipation, rather than other classic symptoms or growth retardation, this study was conducted to evaluate the tTG IgA level in the FC patients.

Methods

This single center case-control study was carried out from 2011 to 2013 on 182 patients aged less than 16 years old and with FC using Rome III criteria; they were referred to pediatric clinics of Zabol University of Medical Sciences. Moreover, 420 healthy children who had annual check-up were enrolled in the present study to be compared to the cases. All subjects were examined precisely and meticulous medical history was obtained. Subjects with preexisting history of CD, thyroid dysfunction, calcium abnormalities, inflammatory bowel disease, IgA deficiency, organic cause for constipation, those with gastrointestinal, endocrine, and metabolic diseases, iron deficiency, liver diseases, renal disorders, fever, or chronic conditions were excluded. Examination for perianal erythema, fresh rectal bleeding, and anal fissures was done.

Rome III criteria in FC encompass the followings:

1- Neonates and toddlers

At least two of the following symptoms must occur for at least one month:

- ≤2 defecations per week
- ≥1 episode per week of incontinence after the acquisition of toileting skills,
- History of excessive stool retention
- History of painful or hard bowel movements
- Presence of a large fecal mass in the rectum, and
- History of large-diameter stools that may obstruct the toilet

2- Children and adolescents

Symptoms must occur at least once per week for at least two months and include two or more of the followings in a child with a developmental age of >4 years with insufficient criteria of irritable bowel syndrome:

- Two or fewer defections in the toilet per week
- At least one episode of fecal incontinence per week
- History of retentive posturing or excessive volitional stool retention
- History of painful or hard bowel movements
- Presence of a large fecal mass in the rectum
- History of large diameter stools that may obstruct the toilet

After night fasting (at least six hours), at 8:00 AM, 5 mL blood was obtained from the study subjects and the serum was immediately separated by centrifuge and these serum samples were held in a -70°C fridge for tTG IgA measurements. For serologic evaluation of TTg IgA, 250 micron of the isolated serum of these samples was used, using commercial recombinant ELISA Kit with normal limit of 20 U/mL tTG IgA.

Statistical Analysis

Categorical and continuous variables were compared between cases and controls using chi-square and *t* tests, respectively. Logistic regression model was applied to estimate the association between potential risk factors and FC.

Results

The subjects were 602 children (mean age 5.1 years; 55.5% boys) who were divided into two case and control groups with 182 (30.2%) and 420 (69.8%) subjects, respectively. Mean age of boys and girls was 5.01 ± 0.171 and 5.23 ± 0.188 years, respectively. In the case group, there were approximately 29.9% males and 30.6% females. In the control group, there were 70.1% males and 69.4% females.

Table 1 shows the results of independent *t* test for the comparison to the control and FC patients. The weights of the cases (17.9121 ± 9.078) and controls (21.039 ± 7.871) were significantly different ($P < 0.001$). Mean of tTG was significantly higher in the case (13.307 ± 21.990) group compared to the controls (6.9405 ± 6.685) (t=5.385; $P < 0.001$). Age of participants in two groups of case and control did not show any difference ($P = 0.564$). Similar factors were

Table 1. Independent *T* Test for Demographic Factors in Groups of Control and Patients With Constipation

Factor	Groups	Mean	SD	95% CI of the Difference		t	*P*
				LB	UB		
Weight	Case	17.9121	9.07750	-4.565	-1.688	-4.269	0.000
	Control	21.0388	7.87101				
	Total	20.0935	8.37100				
tTG IgA	Case	13.3065	21.99080	4.043	8.689	5.383	0.000
	Control	6.9405	6.68477				
	Total	8.8429	13.55590				
Age	Case	4.9857	3.23100	-.70305	.38377	-0.577	0.564
	Control	5.1454	3.06779				
	Total	5.0971	3.11619				
Weight	Male	20.0663	8.09594	-1.41055	1.28812	-0.089	0.929
	Female	20.1275	8.71682				
	Total						
tTG IgA	Male	8.5477	12.92341	-2.85524	1.52575	-0.596	0.551
	Female	9.2124	14.32451				
	Total						
Age	Male	4.9997	3.13256	-0.72084	0.28316	-0.856	0.392
	Female	5.2185	3.09722				
	Total						

compared in sex groups and Table 1 shows the results. Weight, tTG level, and age were the same in two genders. Table 2 shows sex status in tTG IgA levels according to the cut-off point of 20 for negative and positive states. In negative state of tTG (<20), 91.791% were females when this percentage for males was 91.317%. There was no relationship between the levels of TTg IgA and sex (r = 043, $P = 0.884$). The confidence interval for odds ratio (0.527, 1.678) for sex factor revealed that gender plays the role of both risk and protection. Both sex groups had approximately the same chance to have lower tTG IgA level (odds ration [OR] = 0.941); it shows that sex had no effect on tTG IgA level. However, for groups viz case and control, the 95% CI =0.122, 0.404 displayed that being a member of case group would affect the probability of having less than 20 in tTG IgA (OR = 0.222) and it means that the control group had a preservative effect, because a low percentage of the subjects in the case group had a level of tTG IgA less than the cut-off point (20).

Discussion

The results of this study revealed no significant difference between two groups in terms of age and sex, although the weight had a considerable disparity. Similarly, in the studies performed by Dehghani et al[4], there was the systemic review of van den Berg et al, which demonstrated no considerable differences between the genders.[5]

Striking disparity in the weight between two groups could have resulted either from the anorexia in the domain of FC that varies from 10% to 38% in these patients, or from silent undiagnosed CD.[8]

While the CD-presenting symptoms in the childhood include the classic malabsorption syndrome, there are a number of caveats that need to be recognized in the pediatric population.[7,9,10] First is the fact that children with newly presenting CD may not have classical symptoms and signs. It has been proposed that atypical features are mostly found in children. Second is that CD might have a monosymptomatic manifestation such as constipation, and finally the CD patients may be completely asymptomatic and even obese.[9,10]

In a study on 215 patients with CD, Murray et al reported that constipation had a prevalence of 39% (83 cases) at the presentation and before initiating gluten-free diet.[15]

In the present study, mean tTG IgA levels and serological positive subjects for CD (tTG IgA ≥20) evidenced a statistical striked favour for FC patients.

Pelleboer et al performed a cohort study to evaluate the prevalence of CD, hypothyroidism, and hypercalcemia on 370 consecutive children with constipation. Their results showed that CD was significantly higher in patients with constipation; they suggested screening for CD in such patients.[16]

In contrast, Chogle et al according to a retrospective cohort survey that was conducted on 7472 children with a mean age of 7.9 years during 2007 to 2011 concluded that constipation alone did not increase the possibility of CD; therefore, screening for CD was not cost-beneficial.[12]

McNicholl and Egan-Mitchell suggested that a reasonable influencing clinical picture in CD by the factors such as anorexia and the extent of the mucosal damage and constipated stools has more likelihood when the anorexia is prominent.[17]

Some guidelines suggest that patients with functional gastrointestinal disorders (FGIDs) should be screened by the serologic testing for CD; however, it is open to debate that whether CD is more frequent in populations with FGIDs or not.[11]

Cristofori et al reported higher prevalence of CD among children with IBS than among general pediatric population.[18]

In a systematic review and meta-analysis performed by Ford et al, authors found a fourfold prevalence of biopsy-proven CD in the cases with IBS; this study that involved 14 surveys encompassed 2278 patients that had diagnostic criteria for IBS.[19]

In another meta-analysis on 15 studies, Ford documented that biopsy-proven CD is more prevalent among patients with dyspepsia than among controls.[20]

Table 2. Distribution of tTG IgA According to the Cut-off Point of 20 for Sex and Groups

Group	Statistics	tTG		Total	Contingency Coefficient=r	*p*	Odds Ratio	95% CI for Odds	
		<20 (Neg)	≥20 (Pos)					L	U
Sex									
Male	No.	305	29	334					
	%	91.317	8.683						
Female	No.	246	22	268	0.043	0.884	0.941 (m/f)	0.527	1.678
	%	91.791	8.209						
Total	No.	551	51	602					
	%	91.528	8.472						
Groups									
Case	No.	150	32	182					
	%	82.41758	17.58242						
Control	No.	401	19	420	27.925	0.000	0.222(case/control)	0.122	0.404
	%	95.476	4.524						
Total	No.	551	51	602					
	%	91.528	8.472						

Limitations

The limitations of the present study included the single center study and lack of endoscopy and biopsy for positive patients.

Conclusion

Based on the present study, it seems that the patients with FC should be screened for CD by tTG IgA; however, following endoscopic mucosal confirmation is suggested in the serologic CD positive patients.

Ethical Approval

The parents' informed consent was obtained.

Competing Interests

Authors declare that they have no competing interests.

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