EUROPEAN JOURNAL OF BIOMEDICAL AND PHARMACEUTICAL SCIENCES
http://www.ejbps.com

ISSN 2349-8870
Volume: 11
Issue: 11
576-582
Year: 2024

CORRELATION MARSH CLASSIFICATION AND TISSUE TRANSGLUTAMINASE TITER WITHIN PEDIATRIC JORDANIAN CELIAC PATIENTS

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Article Received on 17/11/2024 **Article Revised on 22/11/2024** **Article Accepted on 28/11/2024**

ABSTRACT

Objective: Celiac disease is an immune mediated systemic disorder elicited by ingestion of gluten in genetically susceptible individuals, characterized by variable clinical manifestations, specific antibodies, enteropathy with variable histology staging. The aim of this study to investigate the correlation between tissue transglutaminase (TTG) titter and histology staging according to MARSH classification. **Methods:** Data were collected retrospectively from electronic medical files and the endoscopy archive at Queen Rania Children's Hospital. The study period, from January 2016 to December 2023 January, included a group of 146 Jordanian paediatric patients aged between 4 and 14 years of both genders and confirmed the diagnosis of celiac disease by histopathology and positive TTG serology test, the selected patients varied in their TTG titer level, we checked the correlation between MARSH histology stages and TTG levels. **Results:** The high titter TTG (>100unit) observed with 74 patients (50,7%), 62 patients (83,8%) of them found associated with advance histology grade according to MARSH classification, while 72 patients (49.3%) with low TTG tit(<100**) 54 (75%) of them had advance histology grade. **Conclusion:** advance MARSH histology grading among Jordanian paediatric celiac patients is observed with majority number of both High and low TTG titter.

KEYWORDS: Celiac, Tissue Transglutaminase, Marsh Clasification.

Jordanian Royal medical services.
Pediatric gastroenterology team.

INTRODUCTION

Celiac disease (CD) represents an immune-mediated enteropathy in response to gluten, A permanent sensitivity to gluten resulting in a small-intestinal inflammatory disorder occurring in genetically predisposed individuals belonging to human leukocyte antigen (HLA)-class II specific haplotypes, celiac disease is characterized by a variable combination of elevated titers of celiac-specific autoantibodies, an inflammatory enteropathy with variable degrees of severity, and a wide range of gastrointestinal (GI) and extraintestinal complaints.[1,2] Gluten is a protein found in certain grains, such as wheat, rye, and barley; it is also found in many prepared foods. For people with celiac disease, eating these causes injury to the villi of the small intestine. The villi function is absorbing food and nutrients. When the immune system damages the villi of the small intestine, it can lead to problems absorbing important nutrients from foods; this is known as "malabsorption.". The prevalence of CD is increasing at a remarkable pace during the past few decades.[3-8] Once thought to be a rare condition, affecting no more than 1/10,000 people, thanks to the availability and widespread use of specific and sensitive serological markers, CD is now recognized worldwide as a common disorder, with a prevalence varying between 3 and 13 per 1000.[9] Like most multifactorial disorders, CD is the result of a complex interaction between genes, immune status of the host, and environmental triggers. One of the key diagnostic features of CD is the presence of serum TTG IGA and IgG autoantibodies. The mechanisms leading to their production in CD are unclear. The upregulation and activation of (TTG) in inflamed tissues may generate additional antigenic epitopes by cross-linking or deamidating exogenous or endogenous proteins. However, the most accepted hypothesis for their formation, which explains also their dependence on dietary gluten, is that the enzyme cross-links itself to gluten during the substrate–enzyme interaction.[11]

The tissue damage typical of CD, characterized by villous atrophy and crypt hyperplasia, is due to a profound remodeling of the small intestinal architecture, the intestinal damage seen in CD is described as follows.
Type 0 or pre-infiltrative stage (normal)
Type 1 or infiltrative stage (increased IELs);

Type 2 or hyperplastic stage (type 1 + hyperplastic crypts);
Type 3 or destructive stage (type 2 + villous atrophy of progressively more severe degrees, denominated 3a—partial atrophy, 3b—subtotal atrophy, and 3c—total atrophy).

CD have wide variety of clinical presentations.GI manifestations are due to malabsorption, such as Abdominal pain and distention, Chronic or intermitted diarrhea, and occasionally severe constipation can be the presenting manifestation in a significant number of patients, children, as well as adults.[13] Other presenting GI tract symptoms are vomiting, weight loss, or failure —to severe malnutrition and cachexia. However, overweight or obesity noted, as well documented in the literature.[14] The extraintestinal manifestations be referred to as "atypical".[18] such as Iron deficiency anemia (IDA) reported in between 12 and 69 % of newly diagnosed celiac cases.[19-20,21,22,23] Dermatitis herpetiformis.[24.25] Dental enamel hypoplasia.[26] Aphthous ulcers[27], Joint involvement[28], neurological symptoms include headache[29], peripheral neuropathy[30], and seizures. In another hand theirs a lot of diseases associated with CD, Among of these conditions increased prevalence of CD such as chronic obstructive pulmonary disease[31], ischemic heart disease[32] urticarial[33], eosinophilic esophagitis and gastroesophageal reflux disease[34], pancreatitis[35], hemochromatosis[36], cataracts and uveitis[37,38], idiopathic dilated cardiomyopathy[39], nephrolithiasis[40], end-stage renal disease[41], eating disorders[42], primary hyperparathyroidism[43] adrenal insufficiency[44], systemic lupus[45], cataract[46], IgA deficiency about 8 % of IgA-deficient children are celiac[47] and about 2 % of CD children are IgA-deficient.[48] Another association is autoimmune conditions thought to be mostly due to a shared genetic component in the HLA region. The best described association is with type 1 diabetes mellitus (T1DM), where a prevalence of approximately 10 % of CD is found.[49,50] Hashimoto thyroiditis, autoimmune hepatitis, rheumatoid arthritis, Sjogren's syndrome, inflammatory bowel disease.

Another association is with chromosomal disorders such as Down syndrome[51], Turner syndrome[52], and Williams syndrome[53], are conditions where the prevalence of CD has been found to be higher than in the general population, and hence children with such syndromes need to be screened for CD.

According to the recent guidelines from American college of gastroenterology the confirmation of celiac disease diagnosis depended on a combination of finding from medical history, physical examination, positive serology, and upper endoscopy with histological analysis of multiple biopsies from duodenum. The diagnostic criteria for celiac disease it considered by serological test which fundamental for diagnosis with measuring the serum IGA, IGG antibodies to tissue transglutaminase it recommended as initial testing owing high sensitivity 94% and specificity 97%. and excellent standardization[54], but they not recommend for definitive diagnosis due to possible false negative result. a high titer of IgA may be an associated with severe damage of small intestine mucosa whereas a borderline increase of TTG may be an isolated finding not always associated with active celiac disease. A small Intestinal biopsy is required in most patients for final diagnosis. guidelines from European society (ESPHGAN) for diagnosis of celiac disease without the need for intestinal, depending on symptomatic patient with high titer anti-TTG IgA (more than 10* the upper normal limit) and predisposing HLA genotypes. The small intestinal enteropathy in celiac may be of variable severity. A spectrum of histological signs could be present according to the MARSH classification. The changes, even the most severe, are not pathognomonic and should always be interpreted in the context of the clinical and serological setting. In children with sign and symptoms of celiac disease with high titer of (TTG IGA) levels exceeding 10 times upper limit of normal the likelihood for villous atrophy (marsh 3) is high. Our investigation aimed to determine the correlation between a high titer (TTG) and MARSH classification if almost high titer serology must have always advance histopathological stage, at the same time we checked if low titer TTG is associated with low histopathological stage, serology laboratory test was done to all patients for multiple reasons, as patients have GI and non-GI manifestations suggested of CD, screening for high-risk group to develop CD or family history with CD. after that all patients underwent upper endoscopy and found different histopathological changes seen with celiac patients.

METHODOLOGY

This retrospective statistical analytical study of 146 cases of celiac disease was conducted using data from the archive of the GI endoscopy department at Queen Rania Children's Hospital and patients' medical electronic files (Hakeem) for the period between January 2016 and December 2023., this study was registered by the institutional ethics committee of royal medical services under number of 32/212024. As this study retrospective analysis, the requirement for patients' consent was waved. collected data included 146 pediatric patients diagnosed with celiac disease depend on both positive serology test and duodenal biopsy, the age between 4-14 years, both gender distributions, duodenal biopsies approved histopathological changes found with celiac disease and classified according to MARSH classification to three stages, the serology laboratory test examination TTG IGA and IGG titer observed with variable values for all patients, the patients divided into two group first group with high serology titer above 10 times upper of normal limits (TTG>100 U/ML), and the second group with low serology titer below the 10 times upper normal limits (TTG<100 U/ML).

The inclusion criteria, included patients with GI and non-GI sign and symptoms of celiac disease, patients with high-risk group or family history of celiac disease, positive serology test TTG IGA, IGG with variable values, histological biopsies approved celiac disease changes according to MRSH classification.

The exclusion criteria existence patients with normal duodenal biopsy with positive serology titre, patients with positive serology titre while the duodenal histopathology suggestive celiac disease.

The collected data documented and organized on Microsoft excel worksheet. The statistical analyses were performed using a statistical package for the social science (SPSS) software version 28 for Windows. The categorical data expressed in frequency and percentage while the scale data represented by mean and standard deviation. Chi-square of independence was used to find Association between categorical data in contingency table. A cut-off p-value of 0.05 for Statistical significance was presumed.

RESULTS

A total of 146 children attended the paediatric gastroenterology clinic with different clinical sign and symptoms of celiac disease or with positive serology test TTG. All of them were scheduled for upper gastroduodenal endoscopy, and duodenal biopsies histology confirmed diagnosis of celiac disease. The study included 82 female patients (56%) and 64 male patients (44%). The paediatric age range was from 4 to 14 years, with an average of 9.8 years (SD=2.77)., with the most dominant age being 11 years old (n=20). Furthermore, the patients were divided into two groups after endoscopy and confirmed Celiac disease by both positive serology and histopathology. The first group, G1, included 74 patients, (50.7%) comprising 32 males and 42 females, who high serology titter (>100). The second group, G2, included 72 patients (49.3%), comprising 41 females and 31 males, who have low serology, titter (<100) The distribution of patients' gender according to study groups was not statistically significant, as evidenced by the chi-square test X2=0.642, p=.423 (Table 1).

Table 1: Distribution of patients gender according to study groups.

Gender	Serology value of TTG		Chi-square	p-value
	Low level serology	High level serology		
Females	40 (60.4%)	42 (39.6%)	**0.642**	**.423**
Males	31 (68.1%)	33 (31.9%)		
Total	72	74		

Table 2 shows the different indications to do TTG serology test first represents patients had GI manifestations of Celiac disease (diarrhoea, weight loss, bloating, abdominal pain) Account about 17 patients (11.6%), second patients' group with extraintestinal symptoms like (Anemia, osteoporosis, chronic fatigue, celiac hepatitis, short stature, neurological and behavioral disturbance, and others) and account of 45 patients (30.8 %), and third group patients with positive serology test done as screening of high-risk group to develop celiac disease account about 84 patients (57.5%).

Table 2: clinical manifestations in patients with positive serology test.

PRESENTATION	Frequency	Percentage (%)
GI manifestations	11	11.6%
Extra intestinal manifestations	30	30.8%
Screening	57	57.5%

The prevalence of advance MARSH stage was noted among 116 patients (79.5%) compared to 30 (20.5%) had low MARSH stage. In contrast low TTG serology level was found among 72 (49.3%) compared to 74 patients (50.7%) had high TTG serology level The results presented in table (3) shows the association between MARSH classification and serology levels of TTG (tissue transglutaminase) In the Low-level serology group, 25.0% of patients have a low MARSH score, while 75.0% have an advanced MARSH score. In contrast, for the High-level serology group, 16.2% have a low MARSH score, and 83.8% have an advanced score. However, no significant association between TTG and MARSH classification as evident by Chi-square test X2=1.725, p=0.189.

Table 3: Association between TTG and MARSH classification.

MARSH	Serology value of TTG			Chi-square	p-value
	Low level serology	High level serology	Total		
Low	18 (25.0%)	12 (16.2%)	30	1.725	0.189
Advance	54 (75.0%)	62 (83.8%)	116		
Total	72	74			

The first group with high serology titter was correlated with the MARSH classification of duodenal biopsy which shows about 83.8% patients with high titter had advance stage of mucosal inflammation, while about 16.2% of patient with high titter have low mucosal inflammation. The second group with low serology titter was correlate with the MARSH classification of duodenal biopsy which show about of 75% with low titter has advance stage of mucosal inflammation, and just 25% of patient with low titter have low stage mucosal inflammation.

DISCUSSION

The Queen Rania Children Hospital (QRCH) is a tertiary paediatric hospital in Jordan, considered as referral hospital for many military hospitals at Royal Medical Services and governmental hospitals, as well as from the private sector across Jordan. QRCH treats advanced and complex cases, making our study sample widespread and representative of the entire paediatric Jordanian population.

Among all children included along the period from January 2016 till dec 2023, The screening for high-risk group patients (family history of celiac disease, autoimmune disorder, genetic syndrome) is leading indication for serology testing of celiac disease account about 57.5%, the second indication was patients present with extraintestinal symptoms like (Anemia, osteoporosis, chronic fatigue, celiac hepatitis, short stature, neurological and behavioral disturbance, and others) and account of 30.8 % of cases. and the third indication was patients with celiac GI sign and symptoms account of 11.6%. The diagnosis of CD depends on clinical, serological, genetic, and histopathological parameters. Of these, duodenal histopathology is considered the gold standard. Significant association of anti-TTG antibody titers with the severity of histological grading has been reported in a few of the previous studies.[57,58]

A high titer of anti-TTG serology commonly associated with advance histology grade of celiac disease. ESPGHAN updated guidelines for the diagnosis of CD in the pediatric age group and suggested that children with GI symptoms and having anti-TTG antibody titers 10 times above the normal upper limit with confirmatory positive HLADQ2/DQ8 heterodimer, there are highly likely chances of villous atrophy (MARSH III) and can dispense of doing a histological evaluation for the diagnosis of CD.[59]

In our study we observed and correlated that high serology titer among Jordanian pediatric age group patients were diagnosed with celiac disease is associated with advance histology stage affected intestinal mucosa about (83.8%), in another hand we found small number of patients with high titer above the 10 upper limit (> 100 u/ml) is not associated with advance histology grade (16.2%). There is Significant association between the (TTG) antibodies titter and the severity of histological grading has been reported in a previous study.[57,58] Barker et al. showed that 48 of the 49 symptomatic children with (TTG IGA) antibody titers ≥ 100 U/ml (five times the normal cut-off) had Marsh grading of at least grade II enteropathy with a sensitivity and specificity of 98% and 97.2%, respectively.[59] Allesio et al. confirmed that in patients of all age groups with positive (TTG IGA) serology ≥ seven times the cut-off the probability of duodenal damage is very high, and under specific conditions.[60] Some specific conditions within Jordanian population such as the traditional menu is mainly depended on gluten contain diet and consuming large amounts of gluten daily, in addition the early introduction of gluten in early infancy, and variable immunological response could be an explanation for advance histopathological MARSH grade.

Observation in our study. It gives an insight into the importance of assessing gluten intake in nutritional history while interpreting the anti-TTG antibody titers. Similar findings were also observed in a study by Hawamdeh et al. where 18% of the patients with Marsh grading III had anti-TTG antibody titers less than 10 times the UNL.[61] An inverse association was observed between low TTG titer levels and advance MARSH grading, about 75% patient with low TTG found to have advance MARSH grading This study's limitations include non-evaluation of HLA typing in celiac patients due to this facility's not done routinely for all patients. And assessment the daily consumed amount of gluten.

CONCLUSION

This study demonstrated a significant association between high anti-TTG antibody titers more than 10 times of the ULN and the advance MARSH grade duodenal histological severity in pediatric Jordanian patients with CD. In another hand an interesting finding found within Jordanian pediatric celiac patients that majority patients with low serology titter also associated with advanced histopathological grade according to MARSH classification may this finding due to amount of gluten in diet and immunological response with Jordanian children population. Our recommendation that the high serology titer above 10-time of normal value is associated with advance MARSH histology grade, all patients with high serology marker and done test as screening had advance histological grade, so we can recommend to exclude upper endoscopy with duodenal biopsy for some patients with high risk to do gastroduodenoscopy and confirmed diagnosis depend on positive genotype HLA DQ2,8 On the other hand, all patients with low serology titer < 100 U/ML mandatory need to do upper endoscopy with biopsy taken for histopathology microscopy examination to check the presentation small intestine mucosal changes of celiac disease to confirm diagnosis. Also, our recommendation to decrease the daily consumed amount of gluten in traditional dietary regimens as considered triggering factor, and delay introduction of gluten during infancy

age, especially patients with high-risk group to develop celiac disease.

ETHICAL APPROVAL

An institutional review board approval was obtained from the ethical committee at royal medical services. Patient data privacy and confidentiality are maintained as this study was conducted in compliance with ethical standards per Helsinki declaration.

LIMITATION OF STUDY

The main limitation of our study is the absence testing for detection subepithelial anti-TTG IgA deposits by double immunofluorescence which may be useful in doubtful cases with high serology titer but low histological stage. And estimating daily amount intake of gluten in diet.

ACKNOWLEDGMENT

The authors are grateful to Mrs. Anees Hjazeen (Bio statistician from Jordan) for corporation in statistical work.

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