DOI: 10.7860/JCDR/2024/70668.19743

Original Article

Paediatrics Section

Diagnostic Accuracy of Tissue Transglutaminase and Combined Assay of Tissue Transglutaminase and Deamidated Gliadin Peptide in Children with Coeliac Disease: A Cross-sectional Study

PANKAJ KUMAR YADAV[1], NISHA ATTRI[2], LALIT BHARADIA[3], RAJIV KUMAR BANSAL[4]

ABSTRACT

Introduction: Coeliac Disease (CD) is a systemic immune disorder caused by gluten in genetically susceptible individuals. A serological screening assay for CD has been designed to detect Immunoglobulin A (IgA) and IgG anti-tissue Transglutaminase (a-tTG) and IgA and IgG Deamidated Gliadin Peptide antibodies (a-DGP) simultaneously. The seronegative gap can be closed when these two antigens are combined on a single solid phase. This is primarily because untreated CD children who are negative for antibodies of one of the antigens may exhibit a positive result for the other.

Aim: To determine the diagnostic parameters {sensitivity, specificity, Positive Predictive Value (PPV), Negative Predictive Value (NPV)} of tTG-IgA and htTG-DGP (Coeliac fusion- a combination of IgA and IgG to human tTG and synthetic DGP) for the diagnosis of CD in clinically symptomatic children.

Materials and Methods: This cross-sectional study was conducted at the Paediatric Outpatient Department (OPD) of Santokhba Durlabhji Memorial Hospital, Jaipur, Rajasthan, India from April 2023 to November 2023. The study population comprised 45 children (age >6 months and <18 years) showing clinical features of CD. Considering biopsy as the gold standard, the diagnostic parameters (sensitivity, specificity, PPV, NPV) of tTG-IgA and htTG-DGP were calculated with a 95% confidence interval for both tests. To determine the agreement between the two tests, Cohen's kappa was calculated. A p-value less than 0.05 was considered statistically significant.

Results: Out of the study population, 23 (46%) CD patients were in the age group of 3-6 years, while 13 (26%) patients were in the age group of 6-9 years. A total of 24 (53.3%) CD patients were males, and 21 (46.7%) were females. Chronic diarrhoea was the most common clinical feature in 31 (62%) patients. Considering duodenal biopsy as the gold standard, the study results showed that the anti tTG-IgA antibody test had a sensitivity of 91.1%, specificity of 80%, PPV of 97.6, and NPV of 50%. In comparison, the htTG-DGP antibody test had a sensitivity of 95.6%, specificity of 100%, PPV of 100%, and NPV of 71.43%.

Conclusion: Currently, tTG-IgA is considered the best CD screening test. However, the inclusion of DGP IgG could increase diagnostic sensitivity, and a Combined IgA/G-DGP/tTG assay could be even better than tTG-IgA for the diagnosis of childhood CD.

Keywords: Anti-deamidated gliadin peptide antibodies, Anti-transglutaminase antibodies, Duodenal biopsy, Immune-mediated disease

INTRODUCTION

In genetically susceptible individuals, the gliadin fraction of wheat gluten and similar alcohol-soluble proteins (prolamines) of barley and rye are known to cause damage to the small intestinal mucosa, thereby resulting in CD syndrome [1]. In individuals suffering from this condition, typical CD symptoms such as intestinal malabsorption, chronic diarrhoea, loss of appetite, weight loss, and abdominal distention become apparent within the first two years of life [1,2].

There are several serological tests for CD diagnosis used to detect antibodies targeting fragments of the gluten antigen, such as anti-DGP, or self-antigens like Anti-endomysial (EMA) and anti-tTG antibodies of both IgA and IgG classes [1]. Previously, in children, the diagnosis of CD was primarily based on small intestine biopsy. Currently, with the availability of the latest diagnostic techniques, the CD diagnostic algorithm has significantly changed. The International diagnostic guidelines by the European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) [3]; the North American Society for Paediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) [4]; and the American College of Gastroenterology (ACG) [5] recommend the use of tTG-IgA antibody as the most cost-effective and reliable screening test to identify CD. For patients with selective IgA deficiency who require an IgG-based test (TTG or DGP) [3-5], it is also recommended to check serum IgA levels at the initial testing stage.

There is controversy about the screening algorithm in children below the age of 2 years, primarily due to prevailing concerns about tTG-IgA sensitivity in this age range [6-9]. However, regardless of the age group, ESPGHAN has recommended initial testing with tTG-IgA alone (plus total IgA) [3]. At the same time, NASPGHAN and ACG recommended combining tTG-IgA with DGP IgG to improve diagnostic accuracy in children younger than two years of age [4,5]. There is a strong link between CD and autoantibodies against tTG. Currently, antibodies to DGP-AGA have been included in a wide range of serological tests for CD [4,5]. The DGP (IgA+IgG) screen, which is highly sensitive and specific for detecting active CD, can identify IgA and IgG antibodies in both IgA-deficient and IgA-sufficient patients. DGP, when combined with human tTG, forms a single cost-effective assay with screening ability for CD patients of all ages, including adults, children, IgA-sufficient, and IgA-deficient

individuals [10]. The seronegative gap can be closed by combining the two antigens on a single solid phase. Due to an additive effect, the combination antigen assay shows increased sensitivity as it can detect positive patients with low levels of antibodies to both antigens, just below the positive cut-off value of a single antigen test. Based on these observations, the combined IgA/G-DGP/tTG assay has been recommended as a front-line screening test for identifying childhood CD and as a marker of dietary compliance [10].

In light of the above, the present study was planned to determine the diagnostic parameters (sensitivity, specificity, PPV, NPV) of tTG-IgA and htTG-DGP (a coeliac fusion combining IgA and IgG to human tTG and synthetic DGP) for the diagnosis of CD in clinically symptomatic children.

MATERIALS AND METHODS

It was a cross-sectional study of consecutive eligible patients suspected of having CD who attended the Paediatric OPD at Santokhba Durlabhji Memorial Hospital in Jaipur, Rajasthan, India from April 2023 to November 2023. Ethics committee approval (IEC No. 7528-29) was obtained for the study. Written informed consent was obtained from all caregivers of the children.

Inclusion criteria: Children aged >6 months and <18 years with signs and symptoms suggestive of CD (chronic diarrhoea, abdominal distention, failure to thrive, anaemia), or those referred from other centres for CD confirmation, were included. Children diagnosed with diseases highly associated with CD (such as autoimmune hepatitis, Down syndrome, dilated cardiomyopathy, Type 1 diabetes mellitus, autoimmune cholangitis, autoimmune thyroid disease, primary biliary cirrhosis, etc.) and those with a family history of CD in a first-degree relative were also included.

Exclusion criteria: Children aged <6 months or >18 years were excluded. Children previously diagnosed with CD or for whom a biopsy could not be performed or was contraindicated were also excluded.

Sample size calculation: The sample size comprised 43 subjects at a 95% confidence interval and a 10% relative allowable error, assuming a 90% sensitivity of the h-tTG/DGP assay for diagnosing CD among suspected patients, as was reported in the study by Parizade M et al., [11].

The following formula was used for calculating the sample size

Where, $N=\frac{Z(\alpha/2)p(1-p)}{D^2}$

$Z\frac{\alpha}{2}$=1.96 at 95% confidence interval

p=assumed sensitivity=90%

d=relative allowable error (10% of sensitivity)

The sample size calculated using other diagnostic parameters of both tests was less than or equal to the previously calculated sample size. Therefore, 50 suspected eligible cases (rounded off) were selected for the study.

Study Procedure

Patients attending the OPD or Inpatient Department (IPD) for the evaluation of Gastrointestinal (GI) symptoms such as abdominal distention, abdominal pain, chronic diarrhoea, or constipation, anorexia, vomiting, or non GI symptoms like anaemia, weight loss/failure to gain weight, weakness (early fatigue), skin manifestations of vitamin deficiency, and neurological manifestations suggestive of CD were thoroughly interrogated for a family history of CD, recent diagnosis of type 1 DM, or other associated autoimmune disorders, and Down syndrome.

The tTG-IgA tests were performed using the commercial kit CHORUS tTG-A. This test utilised an immunoenzymatic method for the semiquantitative determination of IgA class antibodies in human blood serum against tTG. The test was based on the Enzyme-linked Immunosorbent Assay (ELISA) principle and was analysed according to the manufacturer's recommendations (negative <12 AU/mL, Equivocal between 12 to 18 AU/mL, positive >18 AU/mL). For present study, a value greater than 18 AU/mL was considered positive, and less than that was considered negative.

A combination of tTG and DGP serology was performed using the commercial kit Inova QUANTA Lite h-tTG/DGP screen. The test is helpful in detecting IgA and IgG antibodies to synthetic Deamidated Gliadin-derived Peptides (DGP) and human TTG (h-tTG) on a semiquantitative basis in human serum. This test was based on the ELISA principle and was analysed following the manufacturer's recommendations (negative <20 EU/mL, Equivocal 20-25 EU/mL, positive >25 EU/mL). For present study, a value greater than 25 EU/mL was considered positive, and less than that was considered negative. The above-mentioned serological diagnostic tests were compared with a biopsy, which was considered the gold standard for present study.

Upper GI endoscopy and duodenal biopsy were performed for cases with positive coeliac serology. For this purpose, four pieces of mucosa were obtained from the second part of the duodenum, while one piece was obtained from the duodenal bulb. These were kept in separate containers. The grading of the damage to the intestine was done using the Marsh-Oberhuber classification [12]. According to this classification, Marsh stage 3 represents the primary feature of CD, and Marsh type 2 is compatible with it (CD); however, in such cases, the diagnosis should be supported by positive serology. If the serological test is negative, after excluding other disorders, CD should be reconsidered. Although Marsh stage 1 is non specific for CD, its diagnosis should also be supported by a positive serological test [12].

STATISTICAL ANALYSIS

The statistical analysis of the results obtained during the present study was conducted using Epi Info version 7.2.1.0 statistical software and Open Epi version 3. In the result analysis, categorical/nominal variables were summarised as frequency and percentage. For analysing the data obtained, Chi-square test/Fisher's-exact test was performed. Continuous/quantitative variables were summarised as mean and standard deviation. Considering biopsy as the gold standard, diagnostic parameters were calculated with a 95% confidence interval for both tests. To assess the agreement between the two tests, Cohen's kappa was also calculated with a 95% confidence interval. A p-value of less than 0.05 was considered statistically significant.

RESULTS

During the current study, a total of 50 study subjects were included, out of which 45 patients were confirmed to be afflicted with CD based on biopsy results.

Out of the total subjects studied, 23 (46%) were in the age group of 3-6 years, followed by 13 (26%) children in the 6-9 year age group. There were more males, with 24 (53.3%) having CD compared to females, numbering 21 (46.7%). No association was found between CD and the gender of the study subjects (p=0.346) [Table/Fig-1].

Age group (years)	Females with Coeliac Disease (CD) n (%)	Males with Coeliac Disease (CD) n (%)	No Coeliac Disease (CD)	Total n (%)
<3	4 (19.04%)	4 (16.67%)	1 (20%)	9 (18%)
3-6	12 (57.15%)	9 (37.5%)	2 (40%)	23 (46%)
>6-9	4 (19.04%)	8 (33.33%)	1 (20%)	13 (26%)
>9-12	1 (4.76%)	3 (12.5%)	1 (20%)	5 (10%)
Total	21 (100%)	24 (100%)	5 (100%)	50 (100%)
Mean±SD	4.86±2.44	5.42±2.79		5.14±2.6

[Table/Fig-1]: Age and gender distribution of study subjects in relation to definitive diagnosis by biopsy.
Chi-square=0.889 with 1 degree of freedom; p=0.346 (Non significant)

Among the GI symptoms observed, chronic diarrhoea was found to be the most common symptom in 31 (62%) patients, followed by abdominal pain in 20 (40%) patients, and anorexia in 13 (26%) patients. Among the non GI symptoms, pallor was found to be the most common clinical feature among 26 (52%) patients, followed by weight loss/non weight gain in 24 (48%) patients, and weakness in 18 (36%) patients [Table/Fig-2].

Clinical features		n (%)
Gastrointestinal features	Chronic diarrhoea	31 (62%)
	Constipation	3 (6%)
	Vomiting	6 (12%)
	Abdominal pain	20 (40%)
	Anorexia	13 (26%)
Others	Weakness	18 (36%)
	Weight loss/non gain	24 (48%)
	Pallor	26 (52%)
	Pedal oedema	8 (16%)
	Clubbing	3 (6%)
Total		50 (100%)

[Table/Fig-2]: Frequency of clinical features among study subjects (N=50).

The present study showed that h-tTG/DGP was positive in 43 (95.6%) out of 45 biopsies confirmed CD patients. h-tTG/DGP was negative in all the biopsy-negative patients. A Cohen's kappa of 0.811 indicated strong agreement between h-tTG/DGP and biopsy results. The tTG-IgA was positive in 41 (91.1%) out of 45 biopsy-confirmed CD patients. tTG-IgA was negative in most (80%) of the biopsy-negative patients. A Cohen's kappa of 0.561 indicated moderate agreement between tTG-IgA and biopsy results [Table/Fig-3].

Duodenal Bx results	h-tTG/DGP results		Total n (%)
	Positive (>25 eu/mL) n (%)	Negative (<25 eu/mL) n (%)	
Positive	43 (95.6%)	2 (4.4%)	45 (100%)
Negative	0	5 (100%)	5 (100%)
Total	43 (86%)	7 (14%)	50 (100%)
	tTG-IgA results		
	Positive (>18 au/mL) n (%)	Negative (<18 au/mL) n (%)	
Positive	41 (91.1%)	4 (8.9%)	45 (100%)
Negative	1 (20%)	4 (80%)	5 (100%)
Total	42 (84%)	8 (16%)	50 (100%)

[Table/Fig-3]: h-tTG/DGP and tTG-IgA results in relation to duodenal biopsy results for coeliac disease.
Cohen's kappa h-tTG/DGP=0.811 (0.539-1.080)
Cohen's kappa tTG-IgA=0.561 (0.294-0.829)

The diagnostic parameters of h-tTG/DGP for the diagnosis of CD were calculated. High sensitivity (95.6%, 95% CI 85.2-98.8%) and specificity (100%, 95% CI 56.6-100%) as well as high diagnostic accuracy (96%, 95% CI 86.5-98.9%) indicated that h-tTG/DGP could correctly identify most of the patients with the disease and correctly exclude most of the patients without the disease. A high PPV of 100% (95% CI 91.8-100%) indicated that a positive test result could be relied upon as evidence of the presence of the true disease. However, the NPV was relatively lower in comparison at 71.4% (95% CI 35.9-91.8%), indicating that a negative test result may not always mean the absence of the disease [Table/Fig-4].

The diagnostic parameters of tTG-IgA were calculated for the diagnosis of CD. A high sensitivity (91.1%, 95% CI-79.3-96.5%) and specificity (80%, 95% CI-37.6-96.4%) and high diagnostic accuracy (90%, 95% CI-78.6-95.7%) indicated that tTG-IgA could correctly identify most of the patients with the disease and correctly exclude most of the patients without the disease. A high PPV (97.6%, 95% CI-87.7-99.6%) indicated that a positive test could be relied upon as evidence of the prevalence of the true disease. However, the NPV was relatively lower in comparison (50%, 95% CI-21.5-78.5%), which indicated that a negative test result may not always mean the absence of the disease and may be wrongly negative in as many as 50% of patients [Table/Fig-4].

Diagnostic parameters of h-tTG/DGP			Diagnostic parameters of tTG-IgA	
Parameters	Value	95% Confidence interval	Value	95% confidence interval
Sensitivity	95.6%	85.2-98.8%	91.1%	79.3-96.5%
Specificity	100%	56.6-100%	80%	37.6-96.4%
PPV	100%	91.8-100%	97.6%	87.7-99.6%
NPV	71.43%	35.9-91.8%	50%	21.5-78.5%
Diagnostic accuracy	96%	86.5-98.9%	90%	78.6-95.7%

[Table/Fig-4]: Diagnostic parameters of h-tTG/DGP and tTG-IgA for diagnosis of Coeliac Disease (CD).

Both h-tTG/DGP and tTG-IgA were found to be positive in 40 subjects, and both were negative in five patients. Cohen's kappa of 0.608 indicated moderate agreement between these two tests [Table/Fig-5].

tTG-IgA results	h-tTG/DGP results				Total	
	Positive		Negative			
	n	%	n	%	N	%
Positive	40	93.02	2	28.6	42	84
Negative	3	7	5	71.4	8	16
Total	43	100	7	100	50	100

[Table/Fig-5]: tTG-IgA and h-tTG/DGP results in study subjects.
Cohen kappa=0.608 (-0.332-0.885)

Most of the biopsy-confirmed CD patients were in Marsh 3c stage (51.1%), followed by Marsh 3a (24.4%) stage and Marsh 3b (22.2%) stage. Only one patient (2.2%) was in Marsh 2 stage. The h-tTG/DGP was found to be positive in most subjects of all Marsh stages present. h-tTG/DGP was found to be negative in one (9.1%) patient with Marsh 3a stage, while only one patient with Marsh 3b (10%) stage was there. No significant difference was observed in h-tTG/DGP positivity across different Marsh stages of CD (p=0.673) examined [Table/Fig-6].

Marsh staging	h-tTG/DGP results				Total	
	Positive		Negative			
	n	%	n	%	N	%
Marsh 2	1	100	0	0	1	100
Marsh 3a	10	90.9	1	9.1	11	100
Marsh 3b	9	90	1	10	10	100
Marsh 3c	23	100	0	0	23	100
Total	43	96.6	2	3.4	45	100

[Table/Fig-6]: h-tTG /DGP in relation to Marsh stage in biopsy confirmed Coeliac disease patients.
Chi-square=2.402 with 3 degrees of freedom; p=0.673 (NS)

The tTG-IgA was found to be positive in all subjects of all Marsh stage 3b and Marsh stage 3c patients. tTG-IgA was found to be negative in one (9.1%) patient with Marsh 2 stage and three patients with Marsh 3a stage. This difference in tTG-IgA positivity across different Marsh stages of CD was statistically significant (p<0.001), i.e., lower Marsh stages were missed by tTG-IgA, but higher Marsh stages were not missed at all [Table/Fig-7].

DISCUSSION

In the present study, out of 50 cases observed, 45 were duodenal biopsy positive patients for CD, and five biopsies were found to be

Marsh staging	tTG-IgA results				Total	
	Positive		Negative			
	n	%	n	%	N	%
Marsh 2	0	0	1	100	1	100
Marsh 3a	8	72.7	3	27.3	11	100
Marsh 3b	10	100	0	0	10	100
Marsh 3c	23	100	0	0	23	100
Total	41	91.3	4	8.7	45	100

[Table/Fig-7]: tTG-IgA in relation to Marsh stage in biopsy confirmed Coeliac disease. Chi-square=18.060 with 3 degrees of freedom; p<0.001 (NS)

negative. Marked villous atrophy was observed in 73.3% of the cases, out of which the majority were in Marsh 3C (51.1%) stages. In a similar study by Vivas S et al., marked villous atrophy (Marsh stage 3b and 3c) was reported in 63% of the examined children, which is almost in agreement with the present observations [13]. Another study by Parizade M et al., showed that tTG-IgA was positive in all subjects of Marsh stages 3b and 3c. tTG-IgA was negative in 1 (9.1%) patient with Marsh stage 2 and three patients with Marsh stage 3a [11].

The results of the present study showed that the anti tTG- IgA antibody test had a sensitivity of 91.1%, specificity of 80%, PPV of 97.6%, and NPV of 50%, respectively, when considering duodenal biopsy as the gold standard. The high sensitivity (91.1%, 95% CI 79.3-96.5%), specificity (80%, 95% CI 37.6-96.4%), and diagnostic accuracy (90%, 95% CI 78.6-95.7%) indicated that tTG-IgA could correctly identify most patients with the disease and exclude most patients without the disease. These study results are in line with a study by Parizade M et al., on 116 children at high-risk for developing CD, which showed that the anti tTG-IgA antibody test had a sensitivity of 92.9%, specificity of 74.2%, PPV of 90.6%, and NPV of 79.3% [11]. Similarly, a high PPV (97.6%, 95% CI 87.7-99.6%) indicated that a positive test result could be relied upon as evidence of true disease.

In considering duodenal biopsy as the gold standard, the values of htTG-DGP antibody test sensitivity, specificity, PPV, and NPV were found to be 95.6%, 100%, 100%, and 71.43%, respectively. A Cohen kappa of 0.811 indicated strong agreement between htTG/DGP and biopsy results. Out of 43 htTG-DGP antibody-positive cases, all patients were considered positive on biopsy for CD (no false-positive cases). In a similar study, Porcelli B et al., (2014) assessed a combination assay (QUANTA Lite TM htTG/DGP Screen) for CD on 41 patients and reported the presence of IgA and IgG antibodies against a-tTG and a-DGP in the examined samples, with test results showing 100% sensitivity and 91.12% specificity [14]. In a comparable study, Wolf AB et al., conducted a retrospective analysis of 149 CD patients, which showed htTG/DGP antibody test sensitivity, specificity, PPV, NPV, respectively were 83%, 82%, 96%, and 98% [15]. Similar to our study, Jaskowski TD et al., tested sera from 111 CD-suspected children, 130 adult patients suffering from Dermatitis Herpetiformis (DH), and 77 paediatric and 49 adult normal control individuals using IgA/IgG anti-tTG/DGP EIA screen. They reported 92.6% sensitivity while 94.3% were specific in paediatric CD, besides detecting one IgA anti-tTG-negative patient (Marsh 3c) who was not IgA deficient [16]. In present study, two out of four ttG-IgA negative cases of CD were detected by htTG/DGP screen [16]. Presently, high sensitivity (95.6%, 95% CI 85.2-98.8%), specificity (100%, 95% CI 56.6-100%), and high diagnostic accuracy (96%, 95% CI 86.5-98.9%) were documented, indicating that htTG/DGP could identify most of the patients with the disease and exclude most of the patients without the disease with accuracy.

Both h-tTG/DGP and tTG-IgA were positive in 40 subjects, and both were negative in five patients. A Cohen's kappa of 0.608 indicated moderate agreement between these two tests. When the possibility of false positive results is close to zero (PPV=100%), in such cases the diagnosis of CD should be based on serology. Although htTG-DGP had a PPV of 100% and could predict the disease with near accuracy, a duodenal biopsy was still needed for diagnosis. Sugai E et al., while examining 161 high-risk CD patients using the new DGP/tTG Screen assay, concluded that this assay is the best for the initial diagnosis of CD, making biopsy avoidable in a good number of patients under different clinical scenarios where combinations of two tests, including a DGP/tTG Screen, are employed for screening [17]. Like this, the study undertaken presently also demonstrates the superiority of the new h-tTG/DGP Screen assay over conventional assays, based on which it can be considered the best initial test for the diagnosis of CD. The results of the study, besides demonstrating the high sensitivity of the QUANTA Lite TM h-tTG/DGP Screen test, also demonstrate its high specificity. However, with regard to the screening tests, it is well known that they show good sensitivity but at the expense of specificity [17].

Based on recent observations, Agardh D found that in their study of 119 children with CD, the seronegative gap can be closed by combining two antigens on a single solid phase [9]. Their findings concluded that the combined IgA/G-DGP/tTG assay had the highest sensitivity of 100%, followed by 97% with IgA-tTG, 95% with IgG-DGP, 91% with IgA-DGP, and only 13% with IgG-tTG [9].

Therefore, the combined IgA/G-DGP/tTG assay can be considered as the primary screening test for identifying CD and as a marker of dietary compliance in affected children.

Limitation(s)

The present study included a higher number of biopsy-positive cases, which did not represent the general population. This may be attributed to a high level of suspicion in the selection criteria. It is rather beyond authors limits to rule out the feasibility of earlier serological tests carried out by external physicians to determine which individuals to refer for biopsy. To reach a more accurate conclusion, there is a need to undertake combination analysis using h-tTG/DGP Screen with IgA a-tTG or IgA a-DGP along with HLA testing from different kit manufacturers. There is a possibility of variation in assessment by different pathologists (individual bias and experience vary from person to person).

CONCLUSION(S)

The results of the present study showed that the htTG-DGP antibody test had a sensitivity of 95.6%, specificity, PPV, NPV were 100%, 100% and 71.43%, respectively considering duodenal biopsy as the gold standard. A combined IgA/G-DGP/tTG assay may be superior to tTG-IgA for identifying childhood coeliac disease (CD). However, when compared to conventional assays, the additional value of the new h-tTG/DGP Screen assay can be considered the best initial test for diagnosing CD in children. It clearly outperforms more conventional assays in this regard.

REFERENCES

[1] Fasano A. Catassi C. Clinical practice. Celiac disease. N Engl J Med. 2012; 367(25):2419-26.
[2] Green PH, Cellier C. Celiac disease. N Engl J Med. 2007;357(17):1731-43.
[3] Husby S, Koletzko S, Korponay-Szabó I, Kurppa K, Mearin ML, Ribes-Koninckx, et al. European Society Paediatric Gastroenterology, Hepatology and Nutrition Guidelines for Diagnosing Coeliac Disease 2020. J Pediatr Gastroenterol Nutr. 2020;70(1):141-56.
[4] Hill ID, Fasano A, Guandalini S, Hoffenberg E, Levy J, Reilly N. NASPGHAN clinical report on the diagnosis and treatment of gluten-related disorders. J Pediatr Gastroenterol Nutr. 2016;63(1):156-65.
[5] Rubio-Tapia A, Hill ID, Kelly CP, Calderwood AH, Murray JA. ACG clinical guidelines: Diagnosis and management of celiac disease. Am J Gastroenterol. 2013;108(5):656-76.
[6] Bürgin-Wolff A, Gaze H, Hadziselimovic F, Huber H, Lentze MJ, Nussle G. Antigliadin and antiendomysium antibody determination for coeliac disease. Arch Dis Child. 1991;66(8):941-47.
[7] Burgin-Wolff A, Hadziselimovic F. Screening test for coeliac disease. Lancet. 1997;349(9068):1843-44.
[8] Lagerqvist C, Dahlbom I, Hansson T, Jidell E, Juto P, Olcén P, et al. Antigliadin immunoglobulin A best in finding celiac disease in children younger than 18 months of age. J Pediatr Gastroenterol Nutr. 2008;47(4):428.

[9] Agarth D. Antibodies against synthetic deamidated gliadin peptides and tissue transglutaminase for the identification of childhood celiac disease. Clin Gastroenterol Hepatol. 2007;5(11):1276-81.
[10] Cataldo F, Marino V, Bottaro G, Greco P, Ventura A, Pediatrica C. Celiac disease and selective immunoglobulin A deficiency. J Pediatr. 1997;131(2):306-08.
[11] Parizade M, Bujanover Y, Weiss B, Nachmias V, Shainberg B. Performance of serology assays for diagnosing celiac disease in a clinical setting. Clin Vaccine Immunol. 2009;16(11):1576-82.
[12] Marsh MN. Grains of truth: Evolutionary changes in small intestinal mucosa in response to environmental antigen challenge. Gut. 1990;31(1):111-14.
[13] Vivas S, de Morales JG, Riestra S, Arias L, Fuentes D, Alvarez N, et al. Duodenal biopsy may be avoided when high transglutaminase antibody titers are present. World J Gastroenterol. 2009;15(38):4775-80.
[14] Porcelli B, Ferretti F, Vindigni C, Scapellaato C, Terzuoli L. Assessment of a combination screening assay for celiac disease. Autoimmunity Highlights. 2011;2:67-71.
[15] Wolff AB, Mauro B, Faruk H. Intestinal biopsy is not always required to diagnose celiac disease: A retrospective analysis of combined antibody tests. BMC Gastroenterol. 2013;13:19.
[16] Jaskowski TD, Donaldson MR, Hull CM, Wilson AR, Hill HR, Zone JJ, et al. Novel screening assay performance in pediatric celiac disease and adult dermatitis herpetiformis. J Pediatr Gastroenterol Nutr. 2010;51(1):19-23.
[17] Sugai E, Moreno ML, Hwang HJ, Cabanne A, Crivelli A, Nachman F, et al. Celiac disease serology in patients with different pretest probabilities: Is biopsy avoidable? World J Gastroenterol. 2010;16(25):3144-52.

PARTICULARS OF CONTRIBUTORS:
1. Juniour Consultant, Department of Paediatrics, Narayana Hospital, Jaipur, Rajasthan, India.
2. Associate Professor, Department of Pathology, GMC Dausa, Jaipur, Rajasthan, India.
3. Consultant Paediatric Gastroenterologist, Department of Paediatrics, SDMH, Jaipur, Rajasthan, India.
4. Head, Department of Paediatrics, SDMH, Jaipur, Rajasthan, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Nisha Attri,
A-84, Akshat Kanota Estate, Kanota, Jaipur-303012, Rajasthan, India.
E-mail: nisha.attri4@gmail.com

PLAGIARISM CHECKING METHODS: [Jain H et al.]
- Plagiarism X-checker: Mar 19, 2024
- Manual Googling: Apr 09, 2024
- iThenticate Software: Jun 26, 2024 (14%)

ETYMOLOGY: Author Origin

EMENDATIONS: 8

AUTHOR DECLARATION:
- Financial or Other Competing Interests: None
- Was Ethics Committee Approval obtained for this study? Yes
- Was informed consent obtained from the subjects involved in the study? Yes
- For any images presented appropriate consent has been obtained from the subjects. NA

Date of Submission: **Mar 18, 2024**
Date of Peer Review: **Apr 05, 2024**
Date of Acceptance: **Jun 28, 2024**
Date of Publishing: **Aug 01, 2024**