OPEN ACCESS

Research Paper

The Correlation of Human Leukocyte Antigen (HLA) Haplotypes with Clinical and Laboratory Profiles of Celiac Disease in Children

Raghad Dawood Najem[1], Arabiya Idan Ali[2], Rabab Farhan[3]

ABSTRACT:

BACKGROUND:

Celiac disease is an immune-mediated enteropathy triggered by the ingestion of gluten in genetically susceptible individuals. Gluten is the major protein component of wheat, rye, and barley, the major predisposing genes are the HLA-DQ2 and DQ8 genotypes found in at least 95% of patients.

OBJECTIVE:

To demonstrate the profiles of coeliac disease (the way in which coeliac disease present, age and sex distribution, endoscopical and histopathological finding) and to analyze the correlation of HLA haplotypes with clinical and laboratory profiles of coeliac disease in children.

PATIENTS AND METHODS:

A retrospective study was done on a group of children and adolescents of ≤14 years old of age, with clinical diagnosis of celiac disease, whom attended the pediatric gastroenterology outpatient clinic of Children Welfare Teaching Hospital in Baghdad city from January 2014-2018.

A records of forty patients were collected and analyzed including clinical examination, blood tests for serum IgA level, Anti-tTG IgA and IgG, HLA typing, and upper gastrointestinal endoscopy and duodenal biopsy.

RESULTS:

The mean age was 8.1 year. Female were 21(52.5%), male were 19(47.5%). Short stature was the commonest chief complaints in 20 patients (50%) , followed by diarrhea and abdominal pain each in 10 patients (25%). The commonest endoscopy finding was normal in 28 patients (70%), histopathological finding Marsh 3 was the commonest in 27(67.5%) patients.

HLA typing system: 15 patients labeled as DQ2 (37.5%), 12 patients labeled as DQ8 (30%) , 12 patients were having both DQ type (30%). The dominant haplotype was DQB1*02 , Anti_tissuetransglutaminase IgA was positive in all of those having both DQ2 and DQ8 100%.

CONCLUSION:

This result showed that patient with severe histopathology (Marsh 3) carried HLA -DQ risk alleles and in other side Marsh 1 or 2 carried low or no HLA-DQ risk alleles, patient with at least one DQB1*02 allele showed high expression of clinical and histological presentation of coeliac disease.

KEYWORDS: Human leukocyte antigen (HLA) haplotypes, Celiac Disease.

[1]*D.C.H., M.R.C.P. (1), FICMS (ped.), FICMS (paed.)GIT . C.A.B.p.Central Teaching Hospital of Pediatric.*
[2]*D.C.H., FICMS (ped.), C.A.B.p.Central Teaching Hospital of Pediatric.*
[3]*Asst. Prof. of Pediatric Consultant Pediatric Gastroenterology College of Medicine/ Baghdad .*

Iraqi Postgraduate Medical Journal, 2024; Vol. 23(3): 270-278
DOI: 10.52573/ipmj.2024.137433 *Received: February 26, 2023, Accepted: July 9, 2023*

INTRODUCTION:

Celiac disease (CD) is an immune-mediated enteropathy triggered by the ingestion of gluten in genetically susceptible individuals. Gluten is the major protein component of wheat, rye, and barley, the major predisposing genes are the HLA-DQ2 and DQ8 genotypes found in at least 95% of patients. [(1)]

CD is characterized by the presence of a variable combination of gluten-dependent clinical manifestations, CD- specific antibodies, HLA-DQ2, DQ8 haplotypes and enteropathy. [(2)]

It can occur at any age, including in babies when weaning once gluten has been introduced to their diet, in children and in adolescence. When a child with celiac disease eats gluten, his or her immune system reacts by damaging the lining of the small intestine. [(3)]

PATHOGENESIS CD is a multifactorial disorder that depends on both genetic and environmental factors for expression.[(4)] Ninety-five percent of patients with CD have the HLA-DQ2 heterodimer, which is encoded by alleles

DQA1∗05 and DQB1∗02, either Cis configuration or Trans, and most of the remainder have the HLA-DQ8 heterodimer, encoded by the DQB1∗0302 allele. [5]

HLA-DQ2 and DQ8 in Celiac Disease Pathogenesis

HLA-DQ2 and DQ8 play crucial roles in celiac disease pathogenesis. HLA-DQ molecules are responsible for presentation of peptide antigens to $CD4^+$ T cells. Peptides presented by class II HLA molecules are derived from degraded proteins found in the microenvironment. [6]

HLA-DQ2 and DQ8 are uniquely able to present specific gluten-derived peptides, where as other HLA types cannot. Before binding to DQ2 or DQ8, though, native gluten peptides are converted to negatively charged particles in the intestine. Tissue transglutaminase 2(TTG2) is responsible for this modification, which is termed deamination. [7]

Antigen-presenting cells then present deamidated gluten bound to HLA-DQ2 or DQ8 to elicit a gluten-specific CD 4^+ T-cell response, initiating inflammation. [8]

So patient of coeliac disease could be:

- **SYMPTOMATIC:** Frank malabsorption symptoms and signs (e.g., chronic diarrhea, failure to thrive, weight loss) or Extraintestinal symptoms and signs (e.g., anemia, fatigue, hypertransaminasemia, neurologic disorders, short stature, dental enamel defects, arthralgia, aphthous stomatitis)
- **SILENT:** No apparent symptoms in spite of histologic evidence of villous atrophy in most cases identified by serologic screening in at-risk groups.
- **LATENT:** Subjects who have a normal intestinal histology, but at some other time have shown a gluten-dependent enteropathy.
- **POTENTIAL:** Subjects with positive celiac disease serology but without evidence of altered intestinal histology. Patients may or may not have symptoms and signs of disease and may or may not develop a gluten-dependent enteropathy later. [2]

DIAGNOSIS

Achieving early diagnosis of coeliac disease is critical to ensuring good lifelong health and providing children with the ability to thrive. [3]

The diagnosis of CD is based on a combination of symptoms, antibodies, HLA status, and duodenal histology.[2]

The initial approach to **symptomatic patients** is to test for anti-tTG IgA antibodies and for total IgA in serum to exclude IgA deficiency.

If IgA anti-tTG antibodies are negative, and serum total IgA is normal for age, CD is unlikely to be

the cause of the symptoms. If anti-tTG IgA antibody testing is positive the patients should be referred to a pediatric gastroenterologist for further diagnostic workup, which depends on the serum antibody levels. IgA anti-tTG decline if the patient is on a gluten free diet. In patients with selective IgA deficiency, testing is recommended with IgG antibodies to tTG. Patients with positive anti-tTG antibody levels <10 times the upper limit of normal should undergo upper endoscopy with multiple biopsies.[2]

In patients with positive anti-tTG antibody levels at or >10 times the upper limit of normal, blood should be drawn for HLA and EMA (endomyeal) testing. If the patient is positive for EMA antibodies and positive for DQ2 or DQ8 HLA testing, the diagnosis of CD is confirmed, a life-long gluten-free diet is started and the patient is followed for the improvement of symptoms and the decline of antibodies. HLA testing is almost always positive; thus, it is possible that HLA testing will not be necessary in the future to establish diagnosis. In the rare case of negative results for HLA and/or anti-EMA in a child with tTG antibody titers >10 times the upper limits of normal, the diagnostic workup should be extended, including repeated testing and duodenal biopsies. [10]

In **asymptomatic** persons belonging to high-risk groups, CD should always be diagnosed using duodenal biopsies. When biopsies are indicated, at least 4 fragments should be obtained from the descending part of the duodenum and at least 1 from the duodenal bulb. The diagnosis is confirmed by an antibody decline and preferably a clinical response to a gluten-free diet. CD is not the only cause for villous atrophy. Gluten challenge and biopsies will only be necessary in selected cases in which diagnostic uncertainty remains.[11]

The serological tests are only reliable if the child is regularly consuming gluten. If gluten has been removed from the diet for more than a month prior to testing, the blood test and small bowel biopsy results may be inaccurate or hard to interpret. [13]

The subject with normal serum IgA and normal tTG-IgA do not need to be considered celiac, given the high sensitivity of the test; however, since it would appear that in the infant and toddler tTG-IgA may not be as sensitive as in later ages, DGP-IgA and DGP-IgG can be measured additionally. [14]

More recently, deamidated gliadin peptides (DGP) antibodies of IgG class have been introduced with a sensitivity and specificity close to IgA anti-tTG. Measurement of IgG-DGP is useful in subjects with IgA deficiency and in young children as this antibody maybe the first celiac marker to become positive. [1]

HLA testing can be used to virtually exclude celiac disease in symptomatic patients who have self-started a gluten-free diet. HLA testing can also be helpful to clarify a diagnosis. For example, in those with equivocal serology or biopsy findings and/or incomplete gluten elimination, HLA testing can be used to rule out celiac disease if HLA-DQ2 or DQ8 is absent and would warrant further testing if DQ2 or DQ8 are found .Genetic testing can be used to identify at-risk individuals, particularly first-degree family members of patients with celiac disease. If a family member tests negative for DQ2/DQ8, further testing is not needed.[12]

Treatment

The only effective treatment for celiac disease is complete removal of gluten from the diet (GFD). Currently; patients with celiac disease should not eat products containing wheat, rye, or barley. Patients usually need to follow a strict GFD for the rest of their lives. No foods or medications containing gluten from wheat, rye, or barley or their derivatives can be taken, as even small quantities of gluten may be harmful.[15]

Removal of gluten (with a reduction to below 20 mg/d gluten intake) from the diet of celiac disease patients will result in symptomatic, serologic, and histologic remission in most patients.[16]

PATIENTS AND METHODS:

Study design

A retrospective study was done on a group of children and adolescents of ≤14 years old of age, with clinical diagnosis of celiac disease, whom attended the pediatric gastroenterology outpatient clinic of Children Welfare Teaching Hospital in Baghdad City from January 2014-2018.

The information were collected from the gastroenterology outpatient clinic files where the patients have been treated and follow up.

Study sample

Forty patients were included as they were aged ≤14 years with clinical diagnosis of celiac disease depend on sign and symptoms and serology written in files.

HLA typing: Done in Genetic Department of AL-Karama teaching hospital in Baghdad .

Possible correlations between HLA haplotypes and clinical and laboratory profiles were assessed.

The two sets of alleles , DQA1*05 - DQB1*02 which code for class Ⅱ MHC DQ2 and the result considered positive when any one of the two alleles was present , DQA1*03- DQB1*03 which code for class Ⅱ MHC DQ8 and the result considered positive when any one of the two alleles was present [6].

Upper Gastrointestinal Endoscopy and Duodenal Biopsy were performed to all patients. Done in Gastroeneterology and Hepatology teaching hospital in Medical City in Baghdad.

Marsh Classification for histopathology was considered as following:

Type **0** or pre- infiltrative stage (normal).

Type **1** or infiltrative stage (increased intraepithelial lymphocytes).

Type **2** or hyperplastic stage (type 1+ hyperplastic crypts).

Type **3** or destructive stage (type 2 + villous atrophy of progressively more severe degree, denominated:

- **3a**: partial atrophy.
- **3b**: subtotal atrophy.
- **3c**: total atrophy [4].

Statistical analysis

Statistical analysis was carried out using Statistical package for social sciences version (SPSS version 24). Categorical variables were presented as frequencies and percentages. Continuous variables were presented as (Means ± SD). Pearson's chi square (X2) test was used to find the association between the categorical variables. Pearson's independent sample t-test was used to find the mean difference between two continuous variables. P-value of ≤ 0.05 was considered as significant.

RESULTS:

This study enrolled 40 children as presumptive cases for coeliac disease.

The mean age was 8.1 year there were 9 patients (6 male, 3 female) 1-5 year (22.5%), 16 patients (7 male, 9 female) aged 5-10 years (40%), and 15 patients (6 male, 9 female) aged 10-14 years (37%).

Female were 21 (52.5%) and male were 19 (47.5%). **(Table 1, 2).**

Regarding the presenting chief complaint, short stature in 20 patients (50%), diarrhea in 10 patients (25%), and abdominal pain in 10 patients (25%) **(Table1)**

Concerning medical history:

Chronic diseases were encountered in two patients (5.0%),(one patient had diabetes, other had hypothyroidism).

Family history of coeliac disease was encountered in three patients (7.5%).

Family history of associated autoimmune diseases was encountered in seven patients (17.5%). **(Table 1).**

This study found no significant association between age and sex distributions **(P> 0.05, table 2)** .

Table 1: Distribution of sampled patients according to inquired personal characteristics and medical history.

Variable	Category	N=40	100.0%
Age Group Mean age = 8.1 year	1 _5yr	9	22.5%
	5-10 yr	16	40.0%
	10_14yr	15	37.5%
Sex	Male	19	47.5%
	Female	21	52.5%
Residence	Baghdad	34	85.0%
	Outside Baghdad	6	15.0%
Chief Complaint	Diarrhea	10	25.0%
	Short Stature	20	50.0%
	Abdominal Pain	10	25.0%
Chronic Disease	Positive	2	5.0%
	Negative	38	95.0%
Family History of	Autoimmune Disease	7	17.5%
	Celiac Disease	3	7.5%

Table 2: Age and sex distribution of studied children.

	Sex				
	Male		Female		
Age Group	N=19	100.0%	N=21	100.0%	P value
1-5yr	6	31.6%	3	14.3%	
5-10 yr	7	36.8%	9	42.9%	0.416
10-14yr	6	31.6%	9	42.9%	

In regards to performed investigations **(table 3)**, the following were observed:

Serum IgA was deficient only in one patient (2.5%), this patient had positive Anti-t TG IgG and Marsh 3a histopathology.

Anti-tissue transglutaminase IgA found positive in 33 patients (82.5%), and negative result in 7 patients, one of them IgA deficient mentioned above, other six, they were included in this study and diagnosed CD, we should depend on EMA Ab and DGP IgG for their diagnosis but because not available so depended on Anti-tissue transglutaminase IgG which was positive in them also depend on histopathology which was Marsh 3 for them and HLA typing which was either DQ2 or DQ8.

Anti-tissue transglutaminase IgG found positive in half the sample (50%).

Histopathological examination revealed the following results:

Marsh 0 in 13 patients (32.5%) considered them as potential CD, Marsh I and Marsh Ⅱ were not observed in any patients , Marsh 3 in 27 patients (67.5%) {Marsh 3a in 18 patients (45%), Marsh 3b in 6 patients (15%), Marsh 3c in 3 patients (7.5 %) }.

So Marsh 3 was the most common histopathological finding.

HLA-DQ typing system:

One patient showed negative result but this patient had positive Anti-tTG IgA positive and had Marsh 3a histopathology.

15 patients (37.5%) labeled as DQ2, 12 patients (30%) labeled as DQ 8 and 12 patients (30%) were having both DQ types.

The haplotype of all of DQ2 was DQB1*02 and the haplotype of all of DQ8 was DQB1*03.

So the most common haplotype was DQB1*02.

Table 3: Distribution of sampled patients according to results of conducted investigations.

Variable	Category	N=40	100.0%
Serum IgA Level	Normal	39	97.5%
	Deficient	1	2.5%
Anti-tissue Transglutaminase IgA	Positive	33	82.5%
	Negative	7	17.5%
Anti-tissue Transglutaminase IgG	Positive	20	50.0%
	Negative	20	50.0%
Macroscopic appearance on OGD	Normal	28	70.0%
	Serrated mucosa	6	15.0%
	Gastropathy	6	15.0%
Histopathology finding	Marsh 0	13	32.5%
	Marsh I	0	0.0%
	Marsh II	0	0.0%
	Marsh 3a	18	45.0%
	Marsh 3b	6	15.0%
	Marsh 3c	3	7.5%
DQ Type	None	1	2.5%
	DQ2	15	37.5%
	DQ8	12	30.0%
	Both	12	30.0%
Haplotype of DQ2	DQB1*02	27	100.0%
Haplotype of DQ8	DQB1*03	24	100.0%

The higher frequency presenting chief complaint of those having either DQ 2 or DQ 8 was short stature (53.3%) in DQ2 and 53.1% in DQ8), while it was abdominal pain in 41.7% of those having both DQ types (2&8). **(Table 4)**.

Table 4: Distribution of sampled patients according to observed DQ type and medical history.

		DQ Type					
		DQ2		DQ8		Both	
Variable	Category	N=15	100%	N=12	N-=100%	N=12	100%
Chief Complaint	Diarrhea	4	26.7%	3	25.0%	3	25.0%
	Short Stature	8	53.3%	7	58.3%	4	33.3%
	Abdominal Pain	3	20.0%	2	16.7%	5	41.7%

Anti-tissuetransglutaminase IgG was positive in 40.0% of DQ2, 33.3% of DQ8 and in 83.3% of those with both DQ types. **(Table 5)**.

Anti-tissue transglutaminase IgA was positive in 66.7% of DQ2, 83.3% of DQ8 and in all of those with both DQ types. **(Table 5)**.

Table 5: Distribution of sampled patients according to observed DQ type and to results of serology tests.

		DQ Type					
		DQ2		DQ8		Both	
Variable	Category	N=15	100%	N=12	N-=100%	N=12	100%
Anti-tissue IgA	Positive	10	66.7%	10	83.3%	12	100.0%
	Negative	5	33.3%	2	16.7%	0	0.0%
Anti-tissue IgG	Positive	6	40.0%	4	33.3%	10	83.3%
	Negative	9	60.0%	8	66.7%	2	16.7%

In regard to histological finding according to DQ type, Marsh 3 in this study was prevalent as 73.3% in patients having only DQ 2 type, 41.7% in patients having only DQ 8 and 83.3 % if having both types together.
Marsh 1 and 2 were not observed regardless the DQ type. **(Table 6)**.

Table 6: Distribution of sampled patients according to observed DQ type and to observing Mach3 on histopathology.

Histopathology finding	DQ Type					
	DQ2		DQ8		Both	
	N=15	100%	N=12	100%	N=12	100%
• March 0	4	26.7%	7	58.3%	2	16.7%
• Marsh I	0	0.0%	0	0.0%	0	0.0%
• March II	0	0.0%	0	0.0%	0	0.0%
• March 3a	5	33.3%	5	41.7%	7	58.3%
• March 3b	3	20.0%	0	0.0%	3	25.0%
• March 3c	3	20.0%	0	0.0%	0	0.0%

The association with having which DQ type could not be verified using statistical tests (Chi- square) as it does not operates optimally in presence of small expected cell size.
Observing Marsh 3 on histopathological examination is significant (P-value 0.045) associated only with having DQ 2 HLA type that 78% of Marsh 3 cases has DQ 2 type against 46% in non-Marsh 3 cases (P <0.05). Other studied associations with Marsh 3 were found not significant in this study (P >0.05) **(table 7)**.

Table 7: Distribution of sampled patients according to of presence of March 3 stage in histopathology and other studied factors.

		Stage on histopathology			
		Marsh 3		Other findings	
Variable	Category	N=25	100.0	N=15	100.0
Anti-tissue Transglutaminase IgA P=0.257	Positive	21	77.8%	12	92.3%
	Negative	6	22.2%	1	7.7%
Anti-tissueTransglutaminase IgG P=0.091	Positive	16	59.3%	4	30.8%
	Negative	11	40.7%	9	69.2%
DQ2 P=0.045	Positive	21	77.8%	6	46.2%
	Negative	6	22.2%	7	53.8%
DQ8 P=0.408	Positive	15	55.6%	9	69.2%
	Negative	12	44.4%	4	30.8%
DQ both 2 &8 P=0.141	Both DQ 2 & 8	10	38.5%	2	15.4%
	Any of DQ2 & 8	16	61.5%	11	84.6%

The distribution of type of DQ (2 or 8 or both) was observed as follow:
The higher proportion of all types of DQ (2, 8, or both) found in age group 5-10 years as following 46.7%, 41.7%, 50.0% respectively (**Table 8**).

Table 8: Distribution of sampled patients according to observed DQ type and to their demographic factors.

		DQ Type					
		DQ2		DQ8		Both	
Variable	Category	N=15	100%	N=12	N-=100%	N=12	100%
Age Group	1 _5yr	4	26.7%	3	25.0%	2	16.7%
	5-10 yr	7	46.7%	5	41.7%	4	33.3%
	10 _14yr	4	26.7%	4	33.3%	6	50.0%

DISCUSSION:

This study showed that the mean age of children with coeliac disease was 8.1 years, this is supported by Nelson pediatric textbook[2] that reported the age at presentation of the disease shifts to later in childhood, also approximate the result (8.2 years ± 4.6months) found by Haluk [20], also approximate the result found by Paul[33] mean age was 8.8 years, and approximate the result (9 years) found by Desilvestri [19].

Female 21 (52.5%) were more affected than male 19 (47.5%), this agree with the result found (female 24, male 19) by Haluk [20] also what found by Zubillaga[23] (59 (44%) were male and 74 (56%) were female}, also what found by Gaiani [24] female 98 and male 57, Martinez [18] found female predominance (62%), and Murry [27] found female predominance (73.8%) male (58.6%).

This study found short stature was the most frequent presenting clinical feature 20 patients (50%), then diarrhea in 10 patients (25%), then abdominal pain in 10 patients (25%), which is supported by what found in pediatric Nelson textbook[2] extraintestinal manifestations increasingly become recognized, this also found by Haluk [20] but in this study considered short stature (61%) as part of classical form of coeliac disease, this finding supported by what found by Zubillaga [23] but in this study considered short stature(38%) as part of atypical presentations.

Concerning medical history:

Found two patients had history of chronic diseases (5.0%), one had hypothyroidism and other had diabetes, this similar to what found in result by Haluk [20] one patient hypothyroidism and three patients diabetes .

Family history of autoimmune disease was present in seven patients (17.5%) which was nearly close to the result of study done by Gaiani [24] showed (13.9 %) of selected patients have positive familiarity of autoimmune diseases.

Family history of coeliac disease in this study was present in three (7.5%) of selected patients, this result is less than Gaiani study [24] which showed appositive familiarity for coeliac disease in 20.4% of her patients , but nearly close to Martinez [18] study which showed family history of coeliac disease in 4.8% of her patients .

IgA deficiency found in one patient (2.5%) which near to what found in result of Zubillaga [23] IgA deficiency in two patients.

This study showed positive Anti-tissuetransglutaminase IgA in 82.5% of patients, this result is higher than Gaiani [24] study in which 69.7% of patients had positive Anti-t TG IgA, but less than Martinez [18] study which revealed positive Anti-t TG IgA in 97% of her studied patients. While Anti-tissuetransglutaminase IgA negative in seven patients, this approximate what found by Colombe [17] the result negative in four patients of 28 patients included in her study.

Histopathological finding showed the majority 67.5% of our patients had Marsh 3 (3a 45% , 3b 15% , 3c 7.5%) of done biopsies , this result is similar to Gaiani [24] study which showed majority (51.1%) have Marsh 3 and also similar to Martinez [18] study which showed villous lesions (Marsh 3b, 3c) was observed in majority of her patients (90%). We found the majority (97.5%) of patients diagnosed with coeliac disease were either HLA_ DQ2 positive (37.5%) the haplotype of all DQ 2 was DQB1*O2, HLA_DQ8 positive (30%) the haplotype of all DQ 8 was DQB1*03, and both are positive (30%), this result is similar to study done Rostami Nejad [29] which showed 96% of cases were carrying DQ 2 and/or DQ 8, also similar to study done by Marginean [5] which revealed 93.8% of patients diagnosed with coeliac disease were either HLA –DQ 2 or DQ 8 positive and similar to Zubillaga [23] study showed over all DQ 2 and DQ 8 comprised 97% of the whole cohort study.

So alleles conferred a significantly increased risk for coeliac disease: HLA_ DQB1*02 and HLA-DQB1*03 present in more than 90% of coeliac disease children as what reported in meta-analyses of Desilvestri [23] showed the strongest genetic association with pediatric coeliac disease for those alleles encoding the B-chain of susceptibility heterodimer and particularly for DQB1*02 have a high risk for developing coeliac disease, also Megiorni F [21], Bjorcks [22], Morina [30], Gudeta [31], and Molina [32], support this and found that children having only one HLA_DQB1*-2 allele without any other DQ 2 or DQ 8 allele show the same risk to develop coeliac disease as children carry heterozygous HLA DQ2 and /or HLA DQ 8 full genotype .

HLA haplotypes result in coeliac disease patients were compared to histopathological findings of Marsh classification, the results of this study showed a statistical significance, with **P-value of o.o45** Marsh 3 with DQ 2 so this result showed that patient with sever histopathology (Marsh 3) carried HLA-DQ risk alleles and in other side Marsh 1 or 2 carried low or no HLA-DQ risk alleles, which was similar to what found by

Kazem[28] and Rostami [29], they found patient with at least one DQB1*02 allele showed high expression of clinical and histological presentation of coeliac disease .

In this study we found higher proportion of those with DQ 2, DQ8 or both aged 5-10 years, but HLA-DQ had no statistical significance which was similar to what found in Haluk [20] no statistical significance among the age group and HLA-DQ, also similar to Murry [27] found lack of gene dosage effect on age at diagnosis.

The higher frequency presenting chief compliant of those having either DQ 2 or DQ 8 was short stature while it was abdominal pain of those having both DQ 2 and DQ 8 but we found no statistically significant correlation between HLA-DQ and clinical presentation which was similar to what found by Marginean [5], Haluk [20], Zubillaga [23] and Gaiani [24], no statistically significant correlation between clinical data and HLA-DQ types.

Anti-tissue transglutaminase IgA was positive in 66.7% of DQ 2 , 83.3% of DQ 8 and in all of those with both DQ types, Anti-tissue transglutaminase IgG was positive in 40% of DQ 2,33.3% of DQ 8 and in 83.3 % of both DQ types, but are statistically not significant, this similar to what found by Tuysuz BI [26], Murry [27], Agardh D.[25], they found the evidence of a correlation between genetic background and serological manifestation of coeliac patient not statistically significant .

CONCLUSION:

1. Most common age at presentation 5-10 year with female pre dominance.
2. Short stature is the commonest presenting feature.
3. HLA correlation:
   - Mainly with age 5-10 year.
   - With short stature.
   - With anti-tTG-IgA.
   - OGD mainly normal.
   - With Marsh 3 on histopathology.
4. Children having only one HLA DQB1*02 allele without any other DQ2 or DQ8 alleles show the same risk to develop coeliac disease as children carry heterozygous HLA DQ2 and/or HLA DQ8 full genotype.
5. This result showed that patient with severe histopathology (Marsh 3) carried HLA-DQ risk alleles and in other side Marsh 1 or 2 carried low or no HLA-DQ risk alleles, patient with at least one DQB1*02 allele showed high expression of clinical and histological presentation of coeliac disease .

REFERENCES:

1. Fasano A. and Catassi C. Immune Eenteropathies. WALKER'S Pediatric Gastrointestinal Disease 6th edition, 2018; 16.1 : 1272-1303.
2. Troncone R. and Shamir R. Celiac Disease. Nelson Textbook of pediatric. 20th edition. 2020; 364.2 : 1991- 96.
3. Deirdre K. , Luisa M. , Koninckx R., et al. Pediatric Coeliac Disease : Earlier Diagnosis for Better Lifelong Health. Journal of Pediatric Gastroenterology and Nutrition .2018;67:e 106.
4. Guandalini S. and Discepolo V. . Celiac disease. In :Stefano Guandalini , Anil Dhawan ,David Branski , editors.Textbook of Pediatric Gastroenterology, Hepatology, and Nutrition . 2016;40: 453 -69.
5. Marginean C. , Melit L. , Mares R., et al .Clinical and biological correlations in coeliac disease in children. National library of Medicine. 2017;96:e 6936.
6. Brown N. , Guandalini S., Kupfer S. ,et al . A clinician's Guide to Celiac Disease HLA Genetics . American Journal of Gastroenterology , 2019;114:1587-92.
7. Saeed A. , Assiri M. , Arshadcheema H. .Coeliac disease in children . Journal of Nature and Science of Medicine .2019;2:23-28.
8. Gabrieli D. , Ciccone F. , Capannolo A., et al .Subtypes of chronic gastritis in patients with coeliac disease before and after gluten_free diet .United European Gastroenterology Journal .2017 ;5:805-10.
9. Wahab R. , Beth S., Jansen P. , et al . Coeliac Disease Autoimmunity and Emotional and Behavioral Problems in Childhood. Pediatrics. 2019;144: e 20183933.
10. Villanueva M ., Oyarzum A ., Leyton B ., et al. Changes in Age at Diagnosis and Nutritional Course of Coeliac Disease in the last Two Decades. National library of Medicine. 2020;12:156.
11. Civak M . , Akarsu M . , Soyturk M . , et al .Prevalence of Coeliac Disease in patients with Inflammatory Bowel Disease in Turkish Population.Gastroenterology Research and Practice . 2019;2019:6272098.
12. King J., windsor J., Coward S, et al. Incidence of Coeliac Disease Is Increasing Over Time : Review Article . American Journal of Gastroenterology . 2020;00:1-19 . Review article.

13. Coeliac Australia Fact Sheet:" Testing and Diagnosis of coeliac disease in children " www. coeliac . org. au /upload / 65701 / u files / fact _sheets /Diagnosis coeliac Disease . pdf.

14. Fludvigsson J. , Bai J., Biagi F., et al .Diagnosis and Management of adult coeliac disease : guidelines from the British Society of Gastroenterology . 2014;63:1-20 .

15. Husby S., Koletzko S. , Szabo I., et al. European Society Pediatric Gastroenterology , Hepatology and Nutrition guidelines for diagnosis of coeliac disease 2019.

16. Bai J. and Ciacci C. World Gastroenterology Organisation Global Guidelines. Celiac Disease. 2017.

17. Colombe B. The DQ2 Allele, DQB1*02:02 , Differentiates mild from severe histology in adult coeliac disease patients . Human Immunology. 2015;76:67.

18. Martinez_ojinaga E. , priete M., Monlina M., et al .Influence of HLA on clinical and analytic feature of pediatric coeliac disease. Biomedcentral Gastroenterology. 2019;19 :91.

19. De silvestri A. , Capittini C., Poddighe D. , et al . HLA_DQ genetics in children with celiac disease . Pediatric Research . 2018;83:564-72.

20. Haluk H., Yildiz M., Sevinc E., et al .The influence of HLA_DQ heterodimer on the clinical and laboratory of patients with coeliac disease . NutricionHospitalaria . 2015;32:2594 -99 .

21. Megiorni F, Pizzuti A. HLA-DQA1 and HLA-DQB1 in coeliac disease predisposition :practical implications of the HLA molecular typing . Journal Biomed Science. 2012;19:88.

22. Bjorck S, Lynch K, Brundin C, et al .Repeated screening can be restricted to at _genetic _risk birth cohorts .Journal pediatric Gastroenterology Nutrition. 2016;62:271.

23. Zubillaga P., Ormaechea V., Carlos J., et al . HLA _DQA1 and HLA DQB1 Genetic Markers and Clinical presentation in Coeliac disease . Journal Pediatric Gastroenterology and Nutrition. 2002; 34:548-54.

24. Gaiani F., Bonaguri C., Picanza A., et al. HLA Haplotypes and Clinical Manifestations of coeliac Disease. Current studies in Nutrition and Food Science . 2020;01:19 -25.

25. Agardh D , Lee HS , Kurppa K , et al .Clinical features of coeliac disease. Pediatrics. 2015;135:627-34.

26. Tuysuz BI , Dursun A , Kutlu T, et al .HLA _DQ alleles in patient with coeliac disease in Turkey . Tissue Antigen . 2001;57:540.

27. Murry J. , Moore S.,Van Dyke C., et al . HLA DQ Gene Dosage and Risk and Severity of coeliac disease. Clinical Gastroenterology and Hepatology. 2007;5:1406-12 .

28. Kazem M., Koushki k., Rostami-Nejad M. The Correlation between HLA_DQ 2 and DQ 8 haplotypes and Abnormal Histology in patients with coeliac disease. International Journal of Analytical, Pharmaceutical and Biomedical Science. 2015;4:2278-46 .

29. Rostami Nejad M , Rostami K , Emami M H , et al . Epidemiology of coeliac disease in Iran. A REVIEW. Middle East J Dig Dis. 2011;3:5-12 .

30. Morina A., Kamenaric M. , Azem M. , et al . HLA Haplotype Association with Coeliac Disease in Albanian Pediatric Patients from Kosovo . Gastroenterology Research and Practice. 2019 ; 7369014 : 1-7.

31. Gudeta A. , Ramelius A., Balcha T., et al. Distribution of HLA-DQ risk genotype for coeliac disease in Ethiopian children . Wileyonlinelibrary.com/Journal/tan. 2020; 96 :681-87.

32. Molina M., Polanco I., Urcelay E. , et al. HLA-DQ distribution and risk assessment of coeliac disease in a Spanish center. REVISTA ESPANOLA DE ENFERMEDADES DIGESTIVAS. 2018;110:421-26.

33. Paul S., KaurSandhu B. , Spray C., et al . Evidence supporting serology based pathway for diagnosis coeliac disease in asymptomatic children from high _risk group. Journal of Pediatric Gastroenterology and Nutrition. 2018;66:641-44 .