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Original Article

Prevalence of DQ2, DQ8 and DR4 Alleles in Iraqi Celiac Patients

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ABSTRACT

Celiac disease(CD) is a chronic small intestinal immune-mediated enteropathy precipitated by exposure to dietary gluten in genetically predisposed individuals, many environmental triggering factors are suggested to participate in its pathogenesis, CD is strongly concomitant with specific HLA class II genes known as HLA-DQ2 and HLA-DQ8 which present in 90-95% of celiac patients and the remaining (5-10%) bears DR4-DQ8 haplotype. Also non-HLA genes my influence susceptibility to the disease but their influence has not been confirmed yet. So that this study aims to determine the distribution of DQ2, DQ8, DR4and non DQ2/DQ8 among Iraqi celiac patients. Sample of 80 Iraqi celiac patients (tTg-A,tTg-G and AGA positive) has been chosen from all suspected patients who attending to Al-Suder- Medical city during the period of April 2015 to November 2015, blood samples were obtained from those patients and send for DNA extraction and HLA typing by RT-PCR. The results showed that 70% (56) patients were females and 30% (24) were males, also 37.5% from those patients were lies between 1-10 years old. HLA typing showed that 77.5% of those were had DQ2 genotyping, 7.5% were had D82 genotyping, 10% were had DR4-DQ8 genotyping and 5% were had non DQ2/DQ8 genotyping.

Key words: *Celiac disease, DQ2, DQ8, DR4.*

INTRODUCTION

Celiac disease(CD) is a chronic small intestinal immune-mediated enteropathy precipitated by exposure to dietary gluten in genetically predisposed individuals.[1] A complex disorder, with environmental and genetic factors contributing to celiac disease etiology.[2] Since early 1960s, studies have provided evidence imply that genetic factors influence the susceptibility of disease, some of these studies suggested the association of celiac disease with HLA class II region,[3] primary association of CD with HLA-DQ locus has been revealed by genotyping study of unrelated CD patients.[4]

Nowadays It is well known that CD is strongly concomitant with specific HLA class II genes known as HLA-DQ2 and HLA-DQ8, which located on chromosome 6p21.[5]

Most of CD patients (90-95%) carry HLA-DQ2 variant DQ2.5 encoded in *cis* by the DQB1*0201 and the DQA1*0501 genes of DR3-DQ2 haplotype or *in trans*, where HLA2.5 molecules are encoded by DQA1*05 and DQB1*02 chains located on different haplotypes, DR5-DQ7 and DR7-DQ2.[4,6] The remaining patients (5-10%) bears DR4-DQ8 haplotype.[4,7] However, many people carry these alleles but don't have CD, thus the presence of these alleles is necessary but not sufficient solitary for the development of the CD. Studies in siblings and identical twins advocate that the contribution of HLA genes to the genetic component of CD is less than 50%.[8] In the other hand only a few percent about (4%) of genetically predisposed individuals whom bearing HLA-DQ2/DQ8 genes evolved CD.[9]

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It is well known that after gluten digestion and absorption, the antigen presenting cell in lamina propria, probably dendritic cell that express HLA-DQ2 or DQ8, present gliadin peptides on their α/β heterodimer antigen presenting grooves to sensitized T-lymphocytes that express the α /β T-cell receptor these lymphocytes then activate B-lymphocytes to generate immunoglobulin, also activate other T-lymphocytes to secrete cytokines.[10] These cytokines may damage enterocytes and induce expression of aberrant HLA class II cell-surface antigens on the luminal surface of enterocytes possibly facilitating additional direct antigen presentation by these cells to the sensitized lymphocytes.[11]

Several non-HLA genes that my influence susceptibility to the disease have been identified, but their influence has not been confirmed.[11,12] Certain study showed that HLA locus has the most important effect (odd ratio 6.23), compared to non-HLA loci which has only limited effects (odd ratios 0.7-1.3), a 39 non-HLA loci represent in about 14% of the genetic variance in CD, compared to nearly 40% for HLA locus.[13] So that this study aims to determine the distribution of DQ2, DQ8, DR4 and non-DQ2/DQ8 among Iraqi celiac patients.

MATERIALS AND METHODS

Eighty Iraqi CD patients have been chosen from all suspected patients who attending to Al-Suder-Medical city during the period of April 2015 to November 2015 were included in this study. The age of those patients ranged from 1 year to 45 years, all patients were undergoing blood sample collection to investigate tTg-A, tTg-G, AGA and HLA typing. HLA typing were done by RT-PCR, by using EliGene Coeliac RT kit, according to instructions of manufacture company EliGene**,** while tTg-A, tTg-G, AGA were done by ELIZA technic according to instructions of kits manufacture company (Aeskulisa).

RESULTS

Eighty celiac patients were involved in this study, 56 of those patients were females and 24 were males, the ages of patients were lie between 1- 45 years old.

Distribution of cases according to the age;

Age distribution of cases showed that 37.5% of cases were lie in age group (1-10 year), 22.5% in 11-20year age group, 20% were lie in 21-30year age group,12.5% in 31-40year age group and only 7.5% of cases were lie in age group >40 years, as shown in Fig 1.

These results show that celiac disease is more prevalent in early childhood than other age groups, also showed that occurrence of celiac disease decline with age ongoing.

DISCUSSION

The results of this study are similar to results that obtained by other researchers, one of studies of celiac disease in Iraqi patients showed that 35.9% of Iraqi patients were at age of less than 10 years.[14] Also this results come in agreement with the results of other study which studded patients with celiac disease in Karbala and showed that 64% of patients were lie in age group 2-10 years.[15] Additionally similar to results of study that involved 509 patients who referred to the immunology department in Baghdad teaching labs and showed that most cases of celiac disease were reported in the age group 1-10 years.[16]

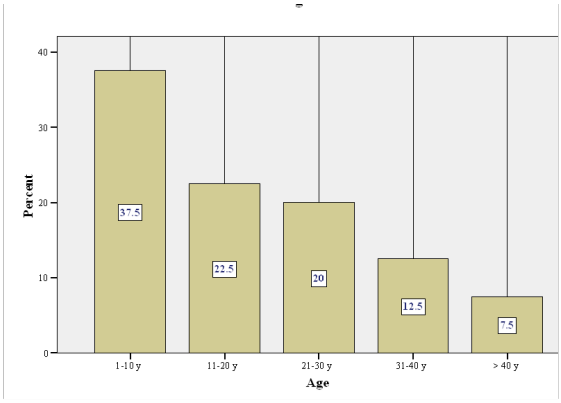

Figure (1) ;Distribution of cases according to the age.

Generally CD in children is higher than other ages, may be due to that introduction of large amount of gluten or gluten exposure without ongoing breastfeeding may increase the risk of getting CD in children,[17] or may due to environmental factors that influence infancy , or latency of CD in adulthood.[18]

Distribution of cases according to the gender;

Regarding to the distribution of cases according to the gender, this study showed that the majority of cases were females (70 %) and 30 % were males, as shown in Fig 2.

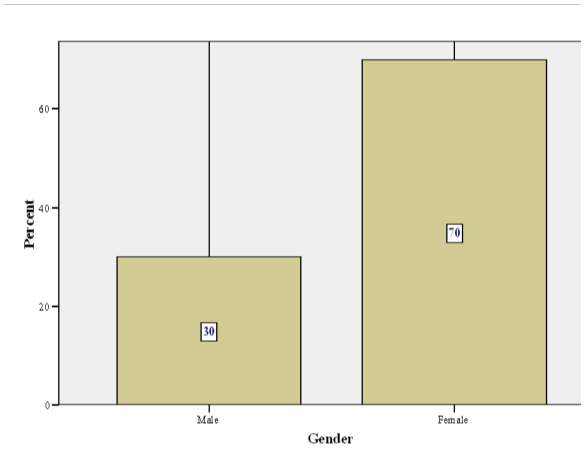

Figure (2): Distribution of cases according to the gender

The results of this study are similar to the finding of Green, when he reported that celiac disease was 2 to 3 times more common in female than in male.[12]

Also, the results of this study come in agreement with the results of other researchers, who showed that the prevalence of celiac disease is 1.5 to 2 times as high among females as among males.[19]

The difference between gender may due to that some genetic loci are gender-influenced and the role of sex hormones in immune response regulation which might

explain these differences,[20] also gender-dependent HLA associations are evident since female patients often carry DQ2.5 and/or DQ8 molecules while DQ2.5/DQ8 negative celiac are frequently males.[21]

Distribution of DQ2, DQ8 and DR4 alleles among celiac patients

HLA-Typing were done by RT-PCR, all celiac patients were tested for the presents or absence of the risky HLA genotypes that represented by DQ2 genotype which encoded by (DQA1*05/DQB1*02) alleles, DQ8 genotype that encoded by (DQA1*0301/DQB1*0302) alleles and DR4-DQ8 genotype that encoded by (DRB1*04) alleles, as well as DQ8 alleles and non DQ2/DQ8 group, that dos not showed neither DQ2 alleles nor DQ8 alleles, As shown in Fig 3, the most prevalent HLA genotype among celiac patients was DQ2 genotype that encoded by (DQA1*05/DQB1*02) alleles, which represented by 77.5%, followed by DR4-DQ8 haplotype (DQA1*0301/DQB1*0302 and DRB1*04) 10% and DQ8 genotype 7.5%, while, 5% of those patients were had none of DQ2 or DQ8 alleles. So that 95% of Iraqi celiac patients have DQ2 and/or DQ8 genotype (77.5 have DQ2 alleles and 17.5 have DQ8 alleles) and 5% have no DQ2 or DQ8 alleles.

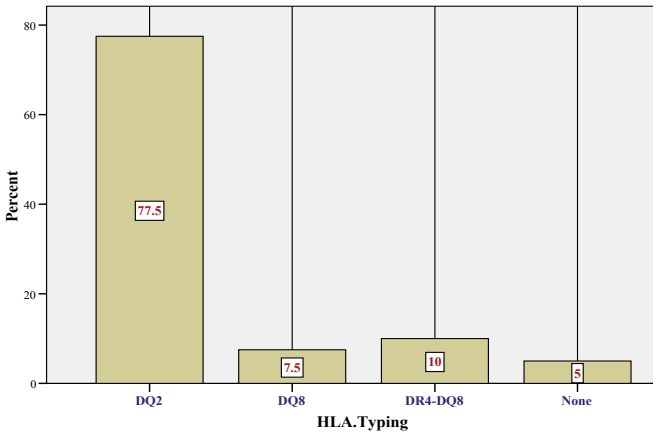

Fig 3. Distribution of cases according to HLA-Typing groups.

The findings of this study are come in agreement with most published world studies which stated that approximately ninety (90) % of celiac subjects present HLA-DQ2 heterodimer, encoded by DQA1*05 and DQB1*02 alleles.[22]

Also, HLA DQ8 (DQA1*0301 and DQB1*0302) is less strongly associated with CD in the Middle East and North American countries.[23]

In addition, the results obtained by this study are come in agreement with results that obtained by Çakır and his coworkers when they studded the accuracy of HLA-DQ genotyping and IgA anti-tissue transglutaminase for the diagnosis of celiac disease in Turkish children and showed that 79.3% of celiac children were had DQ2 genotype and 17.9% of those children had DQ8 genotype.[24]

Farther, the results of this study are agree with the results that obtained by Abdullah & Amina (2012), when they studded the association of celiac disease with HLA-DRB1and HLA-DQB1 alleles in Iraqi patients and showed that DRB1*04 alleles were present in 14% of those patients,[25] and agree with other study which showed that HLA DQ8 (DQA1*0301 and DQB1*0302) is less strongly associated with CD.[26]

Additionally, the results of this study are similar to the results that obtained by Mostafa and his assistants when they studded the signature of HLA class II genes in celiac Sudanese patients and found that frequency of HLA-DQB1*0201 allele (HLA-DQ2) was found in 81.4% of Sudanese celiac patients, while, HLA-DQB1*0302 allele (HLA-DQ8) was seen in 17.14% of those patients.[27]

CONCLUSION

1. Celiac disease occurs in children more than other ages, and more in female than in male
2. DQ2 genotype is the most prevalent HLA genotype among Iraqi celiac patients.
3. DRB1*04 alleles have a role in celiac disease development.
4. Negative result of DQ2 and /or DQ8 don't rule out celiac disease.

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