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Original Research

HLA-DQ2 and HLA-DQ8 Genotyping in Indian Celiac disease Patients and Their First-Degree Relatives

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Abstract

Background and Aim: Celiac disease is a human leukocyte antigen (HLA) associated disease. Approximately 90% to 95% of patients with celiac disease carry the HLA-DQ2 allele and the remaining 5% to 10% carry the HLA-DQ8 allele. Single centre observational study was carried out to determine the role of HLA DQ2/8 testing in screening of first-degree relatives of patients with Celiac disease.

Methods: fifty confirmed patients with Celiac disease and 146 first-degree relatives (parents and siblings) were enrolled. HLA DQ2/8 testing was carried out in all index Celiac disease cases. Clinical evaluation with human Ig A-tissue transglutaminase (Ig A- T tG) and HLA DQ2/8 testing was carried out in all first-degree relatives. Those patients are positive for IgA-TtG were recommended UGI endoscopy and biopsy to document histological changes of Celiac disease

Results: sixteen first-degree relatives were positive for IgA-tTGA and underwent UGI Endoscopy and biopsy and fourteen subjects had histological changes suggestive of Celiac disease . The prevalence of histologically confirmed Celiac disease in first degree relatives were 11.11%. The prevalence of potential Celiac disease was 12.6%.Fourty seven (94%) index cases of Celiac disease and all IgA- t TGA positive first degree relatives were positive for HLA DQ2. None of the index Celiac disease cases or first-degree relatives were HLA DQ8-positive. A total of 86.30% of the first-degree relatives were positive for HLA DQ2 and risk of developing Celiac disease .

Conclusions: 11.11% of the first-degree relatives have CD. Only 13.7% of the first-degree relatives were negative for HLA DQ2/DQ8. Initial evaluation with HLA and serology followed by only serial serology in HLA-positive first-degree relatives is recommanded .

Keywords - HLA-DQ2 and HLA-DQ8, Celiac disease Patients.

INTRODUCTION

Celiac disease is a common food-induced enteropathy that affect approximately 1% of the world's population.[1] The disease is screened by serology, intestinal biopsy , however the sensitivity of serologic tests varies among different laboratories.(2,3,4, 5). Although the disease is triggered by ingestion of gluten, studies have showed that it occurs in genetically susceptible persons(6). Among different studies have shown strong association of celiac disease with HLA class II genes, as HLA-DQ2 and HLADQ8(7). HLA-DQ molecules present in gluten peptides to antigen specific CD4+ T lymphocyte inducing inflammatory reaction to causing the disease(8,9).

Two types of HLA-DQ2,as HLA- DQ2.5 and HLA-DQ2.2. The earlier type is coded by HLA-DQA1_0501 and HLA-DQB1_0201 has strongest association of CD,HLADQ8 is coded by HLA-DQA1_301 and HLADQB1302(10-15). In patients with atypical histologic changes, HLA-genotyping can be useful since the absence of both HLA types can exclude the diagnosis of CD(16). CD is prevalent in the first-degree relatives of patients with CD and it has been found to be 4.8% [17]. Book, Farre et al has shown that the siblings (7.2%) are more affected than the parents (1.8%) [18,19]. Most patients are carriers of the HLA-DQ2/DQ8 genes but these genes are also present in about 40% of the general population, and only a smallpercentage (2-5%) develops CD [20,21]. This indicate that the HLA-DQ genotype is necessary but not solely responsible for the development of the disease.

AIMS AND OBJECTIVES

METHODS

STUDY DESIGN

Patients admitted in the Gastroenterology ward or attending the Gastroenterology OPD were enrolled . Celiac disease patients not having any exclusion criteria. Single centre observational study in Gastroenterology

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Department,Government Medical College And Associated Groups Of Hospitals Kota Rajasthan , India was enrolled as index cases. All participants were informed about the study and written consents were obtained from both the patients and first degree relatives. Blood sampling was carried out for HLA DQ2/DQ8 Genotyping and IgA-t TGA assay.

HLA DQ2/DQ8

To Perform HLA-genotyping, 2ml of intravenous blood was drawn from all participants. DNA was extracted by a rapid genomic DNA extraction procedure and stored at -20°C. HLA-genotyping for all participants was performed using polymerase chain reaction (PCR) to determine the prevalence of HLA- DQ2 (DQB1*02) and HLA-DQ8 (DQB1*03).

IgA tissue transglutaminase antibody

IgA-TtG was measured at 450 nm by ELISA. IgA-TtG titers
< 3U/ml were taken as negative, 3–10 U/ml as borderline and
>10 U/ml as positive.

Intestinal biopsy

All first-degree relatives those are positive for the IgA-TtG to carried out UGI endoscopy+D2 biopsy to rule out CD and send for histological evaluation. Any first-degree relative those are serologically-positive andduodenal histology showed Marsh 2&III (villous atrophy) was labeled as a new CD case. Appropriate dietary counseling with initiation of a gluten-free diet and they have regular follow up. The study was approved by our Institutional Ethics and Research Committee

RESULTS

TABLE: NO. 1
Baselinecharacteristics of the study population (index case)

Variables	No	%
Mean Age (in years)	11.47±8.46 (1.5 to 35 years)	
Gender		
Female	24	48
Male	26	52
Clinical Features		
diarrhea	47	94
Generalized Weakness	32	64
Joint Pain /Myalgia	11	22
Abdomen Distension	10	20

Fifty children (26 boys and 24 girls with male to female ratio 1.08:1),mean age 11.47±8.46 (range1.5 to 35 years) with Celiac disease were enrolled as index cases. The most common clinical presentation was diarrhea (94%) followed by generalized weakness (64%). All were IgA-TtG tissues trasglutaminase antibody positive, had histology suggestive of CD (Marsh I - 6%, Marsh II 4 0%, Marsh III-A 20 %, Marsh III-B -12%, Marsh IIIC-18% and all had shown a definite response to a gluten-free diet. In Upper GI Endoscopy D2 Scalloping Present in 74% cases , Fold Height decreased in 10% cases , Fold Height decreased with nodularity in 6% cases and nodularity in 6% cases and rest 4% cases were normal and Ninty four percent index cases were HLADQ2/2.5 positive .No cases were present with HLA DQ8 .The IgA TtG titre more than 100 were observed in 70% cases

Table: No. 2
HLA DQ2 and DQ8 distribution among index cases and their first-degree relatives

≥100	35	70	1	2.33	5	11.6	4	13.33	6	20	16	10.95
Upper GI Endoscopy												
Fold height decreased	0	0	1	2.33	0	0.00	3	10.00	0	0.00	4	2.74
D2 scalloping present	0	0	0	0.00	5	11.63	1	3.33	6	20.00	12	8.22

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Biopsy												
Normal	0	0	42	97.67	39	90.70	26	86.67	24	80.00	131	89.73
Chronic Duodenitis	0	0	0	0.00	0	0.00	0	0.00	1	3.33	1	0.68
Marsh-II	0	0	0	0.00	0	0.00	0	0.00	3	10.00	3	2.05
Marsh III-A	0	0	1	2.33	0	0.00	1	3.33	2	6.67	4	2.74
Marsh-III-C	0	0	0	0.00	4	9.30	3	10.00	0	0.00	7	4.79

There were a total of 146 first-degree relatives (86 parents, 60 siblings) of these index cases and of these, were enrolled in the study. Seven parents could not be enrolled.146 first-degree relatives evaluated, 86were parents (43fathers ,43 mothers and 60 were siblings [30 brothers and 30 sisters] . IgA-TtG level was >100 in 16 (10.95%) first-degree relatives. In the **Upper GI Endoscopy ,** Fold height decreased in 4 /146 (2.74% cases) and D2 scalloping were present in 12/146(8.22%) in first-degree relatives. Duodenal histology were normal in 89.73 % relatives (and 1 sibling with Chronic duodentis (Table No 2) Among the first degree relatives 9.59 % were Biopsy proven CD -positive and parents were 1 mother and 4 father (5/43 =11.6%) and among the siblings 4 brother and 5 sister(9/60 =15%) were presented with Biopsy proven CD (Table No 3)

Biopsy proven status of relatives									
Mother (N=43)		Father (N=43)		Brother (N=30)		Sister (N=30)		Overall (N=146)	
No	%	No	%	No	%	No	%	No	%
1	2.33	4	9.30	4	13.33	5	16.67	14	9.59

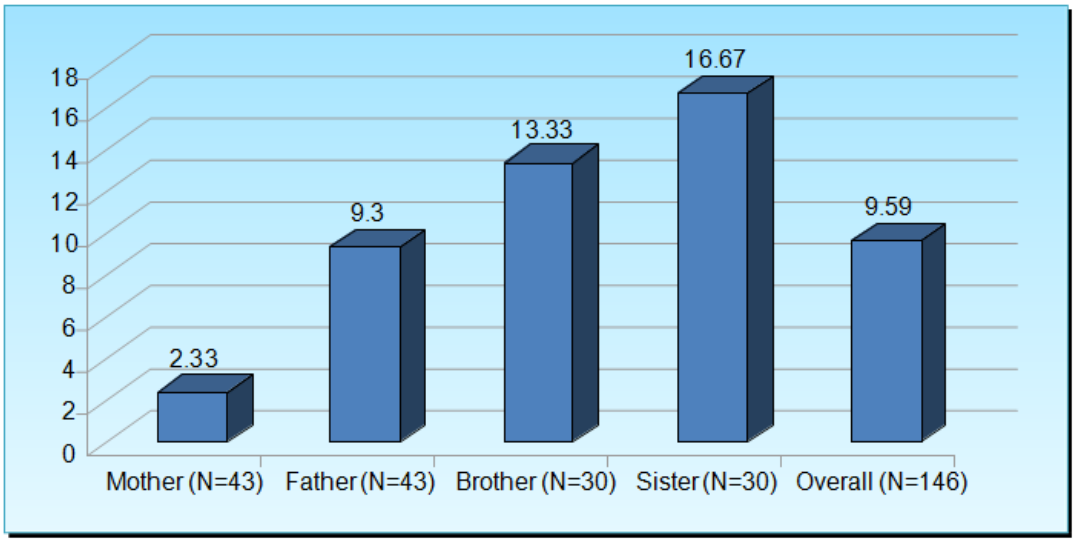

Table :NO.3

Prevalence of CD predisposing haplotype and CD in relatives

	CD (histological confirmed)	HLA DQ2/2.5	Total
First degree relative(N=146)	14(11.11%)	126(86.30%)	146
Parents(N=86)	5(6.85%)	73(84.88%)	86
Sibling(N=60)	9(16.98%)	53(88.33%)	60

Among the first degree relatives(146) , 86.03 % were HLA DQ2/2.5 -positive , parents were 84.88% and siblings were 88.33% presented with HLA DQ2/2.5 –positive status . None were with HLA DQ8-positive. Out of HLA DQ2/2.5 –positive,biopsy proven status of CD were11.11%(14/126) in the first degree relatives. Among parents , (6.85%) 5/73 , and among siblings 9/53(16.98%) were presented with biopsy proven status of CD among the HLA DQ2/2.5 – positive.

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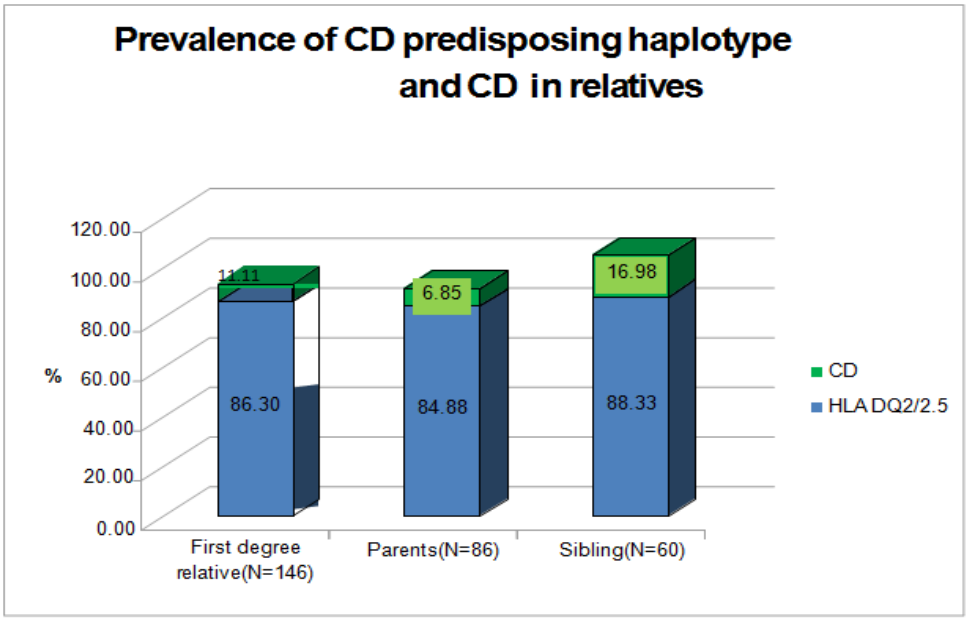

DISCUSSION

In our study most common clinical presentation was diarrhea(94%) followed by generalized weakness(64%) . Prevalence of CD was 11.11%(histology and serology both positive)and the extended CD prevalence on the basis IgA-tTGA and HLA DQ2 positivity was 12.6% irrespective of normal or abnormal histology. In North India a population prevalence of 0.32% (1 : 310) of symptomatic CD in school-going children is reported[24]. Anshu srivastava, Surender Kumar yachha et al. a prospective study has shown total of 85% of the first-degree relatives were positive for HLA DQ2[25]. Our study has shown total of 86.30% HLA DQ2 positive in the first –degree relatives. The prevalence of biopsy-proven CD in first degree relatives ranging from 2.8% to 12% and serology positive ranging e from 5.8% to 14%[26,19,27– 29,30–36]. Our study has shown biopsy proven CD in 11.11%,serology positive 12.6% in first degree relatives. A higher prevalence in siblings as compared to parents has been observed by some authors[37,19]. In our study CD is significantly more frequent among siblings (16.98%) than parents (6.85%).In one study from North India, 9.9% of the control population was HLA DQ2-positive[38]. The DQ2 positive of 86.30% among our first degree CD relatives is average 4.5–8.5 times higher than general north Indian population. Other studies has shown 59% to 73% of all first-degree relatives to be positive for HLA DQ2/DQ8[19,27-29]. Our figure of 86.30% is higher than other studies due to higher enrollment . HLA DQ2/DQ8 was negative in 15.12% of parents and 11.67% of siblings and approximately 13.7% of all first-degree relatives in our study. The two studies of HLA DQ2/DQ8 prevalence in CD from North India has shown 93% and 97.1% of cases to be HLA DQ2- positive, respectively, and none to be DQ8-positive[39,40] In our study, 47/50 (94%) index cases were HLADQ2.5/DQ2 positive.In a large European genetic study of CD has shown 5.6% (57/1008) of CD cases had only one of the DQ2 alleles, HLADQA1*05 or HLADQB1*02[41]. Clinicians should consider the presence of one half of the DQ2 heterodimer as compatible with the diagnosis of CD and it is very rare for CD to occur without one of these genotypes. Kaur et al. has showed that 35 CD cases, 34 were HLA DQ2-positive[40]. In our study has similar finding. The absence of HLA DQ8 in our CD cases is similar to previous Indian studies[39,40]. A Spanish study has showed that 92.4% of CD cases were DQ2-positive and no positive DQ8[41]. Johnson et al. has showed that the DQ8 allele was more prevalent in the New York CD cohort as compared to the Parisian CD cohort [42]. This variationin DQ8 positivity in CD cases may be due to difference in genetics in different population. We also recommended to inclusion of HLA DQ2/DQ8 testing in screening of first-degree relatives. Bonamico et al. were doing HLADQ2/DQ8 tests only in relatives who are serology-negative at the first time and repeat serological screening only in the HLADQ2/DQ8- positive relatives[27].

Conclusion:

11.11% first-degree CD relatives were diagnosed to have CD. New cases were more identified in siblings than parents . one-time HLA DQ2/8 testing along with serology in HLA-positive subjects may also useful for diagnosis and follow up of CD relatives. Early diagnosis and a prompt treatment following a gluten free diet could prevent the development of a clinically severe CD and/or comorbidity and an early identification of first-degree relative at risk leads to primary prevention.

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