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Class II Human Antigen in Iraqi patients with Hodgkin's Lymphoma

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Abstract :

Objective: To detect the association between human leukocyte antigen) HLA) class II and Iraqi patients with Hodgkin's lymphoma (hl).

Subject and methods: Study groups include 80 newly diagnosed Hodgkin's lymphoma patients and two control group patients control which include 50 patients who were newly diagnosed to be affected by non Hodgkin's lymphoma (NHL) and healthy individuals. Antibody mediated complement dependent cytotoxicity assay was done by treating sample of patients lymphocytes with a panel of anti-HLA antisera and complement.

Results: The frequency expression of hla-dr3 and DQ1 was significantly greater in Hodgkin's lymphoma patients than healthy control group with ($p<0.001$) for HLA-DR3 and ($p<0.005$) for DQ1.

Conclusion: Hla-dr3 and dq1 are more related with Hodgkin's lymphoma in Iraqi Arab population that reflect HLA alleles have immunogenetic factors of predisposition to Hodgkin lymphoma

Keyword:

class II HLA, MHC, Hodgkin's lymphoma, lymphoma.

Introduction:

Hodgkin lymphoma(HL) is a lymphorticular disease that was first recognized by Thomas Hodgkin in 1832 who noted enlarged lymph nodes in patients not attributable to inflammation since then there has been a continual subcalssification of the malignant lymphoma ,most notably into Hodgkin's and non Hodgkin types(cancer group institute 2003)

Type of human leukocyte antigen has a possible genetic influence on incidence patterns in HD patients which is a pathogen – processing component of immune function that is highly polymorphic with distribution varying by race and ethnicity (browning et all ,1996).

In Iraq, among the common malignancies HL comes in the tenth rank with male mixed cellularity pattern predominant for the years 1986-1997(ministry of health ,1993,1996 and 1999), while in gulf countries and south east governorate of Yemen ,HL comes in fourth common cancer (Rabadi ,1987; Ezzata et al.,and Bawazir ,1998).

The major histocompatibilty complex (MHC) refers to the Genetic region containing the genes encoding "tissue antigens " or "tissue type" these genes were first identified functionally in rodent as being the factors responsible for rejection of tissue grafts between unmatched individuals .in human, this MHC region lies on the short arm of chromosome six ,and is called the HLA region ,for human leukocyte antigen (strominger at .,1995)the human leukocyte antigen classes (HLC) region has been subdivided into class I, class II , and class III , regions(hyte,2000).

Class II antigens are constitutively expressed on B cells ,monocytes ,dendritic cells, antigen activated T lymphocyte epithelial and endothelial cells ,and it can be induced during inflammation on many other cell types which normally have little or no expression(Thompson et al.,1998) the DQ and DP antigens each have polymorphic alpha and beta chains ,which can dimerize in various

Combinations. in contrast ,DR dimmers all share an essentially invariant alpha chain, while the beta chain carries the extreme polymorphism characteristic of these antigens (Bodmer et al.,1995).

The relationships between HLA and diseases are influenced by linkage disequilibrium ,in such case when a specific allele of one locus is inherited ,generally it is closely linking to specific alleles of other loci on the some chromosome ,for example when DR3 is present in caucasian,A1,B8 ,and DQ2 often accompany (Thompson et al.,1998) strong arguments supporting a genetic linkage between susceptibility to HL and HLA antigens (hors et al.,1983)moreover, other studies denote that HD is determined by both an HLA –associated major gene and other non HLA genetic factors together with environmental effects (shugart et al .,2000).

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Material and method:

Patients: Across sectional study was conducted in the following study group .the patients include in this case –control study were classified into 2 group patients and control group.

Eighty newly diagnosed HL patients (32 female and 48 males) who were either attending the institute of radiology and nuclear medicine or admitted to Al- Mansour and Baghdad teaching hospital in Baghdad city.

All patients were in their new onset of the disease (not on chemo or radiotherapy) at which the histopathological samples were taken and diagnosed as HL according to the national cancer institute working formula, all patients were subject to personal interview using especially designed questionnaire format.

Control groups were age, sex and ethnic matched patients group they were consisted of two group patients control which include 50 patients who were diagnosed to be affected by NHL and healthy control which include 50 healthy individuals whom were not complaining of any malignant problem.

Methods:

Ten ml venous blood were draw from each subject(patients. patients controls and healthy controls) .the blood was dispensed into plastic or glass universal tubes containing either lithium heparin (10 Iu/Ml blood) as anti-coagulant or glass beads followed by a gentile mixing for HAL typing.

Typing HAL-DR and DQ antigens was carried out in the tissue typing laboratory AL- -karam hospital, and in the teaching laboratories of medical city in Baghdad. the test microlymphocytoxicity was established by(Terasaki and Maclelland ,1964) and modified by (Dick et al.,1979 and bender ,1984).

Antibody –mediated complement dependent cytotoxicity assay was done by treating sample of patient's lymphocyte with a panel of anti-HLA antisera and complement.

Anti- HLA sera reacted with the corresponding lymphocyte antigens without visible cell alteration .the addition of rabbit complement leads to a change in the structure of lymphocyte cell membrane which can be made visible by means of an indictor vital dye(eosin) the lysed and vital lymphocytes are assessed using an inverse phase contrast microscope.

The significance of an association between HLA alleles and both patients and control calculated using the Chi-square test with Yates correction as well as fisher exact test (dorak et al.,2002).

Result:

In the study, the HLA class II (DR and Q) allele frequency was determined by microlymphocytotoxicity assay in 2 group of lymphoma Iraqi patients.

the first group include 80 patients with HL, while the second include 50 individuals with NHL consider as patients control .their allele frequencies were compared with 50 healthy controls .the HLA frequencies were compared by fisher exact test.

To determine the strength of association between HLA specificities and disease ,the relative risk (RR) ,etiological fraction (EF) ,preventive fraction (PF) and type of association were estimated the frequencies of class-II HLA antigens (%RR,P,EF,PF and type of association) are show in table(1,2,3 and 4). Three antigens showed increased ,frequencies in the HL patient compared with healthy control. they were DR3 (36.3 versus 10%) DR10 (22.5 versus 8%) and DQ1 (35 verse 18%) The RR value of such association were 4.7,3 and 2.3 respectively while EF values were 0.286 ,0.151 and 0.207 respectively. these difference were significant and the P values were 0.0006 ,0.025 and 0.027 respectively (table 1,2).

Comparing HL patients with NHL patients

Table 1: frequency of HLA-DR antigens of Hodgkin lymphoma patients and healthy control

HLA-DR antigens	Healthy control no.50		HL-patients No.80		RR	P	EF	PF	Type of association
1	7	14.0	9	11.3	0.7	NS	---	0.032	NA
2	8	16.0	6	7.5	0.4	NS	----	0.088	NA
3	5	10.0	29	36.3	4.7	0.0006	0.286	----	PA

4	12	24.0	18	225	0.9	NS	----	0.065	NA
5	5	12.0	2	2.5	0.2	NS	----	0.082	NA
6	3	6.0	1	1.3	0.4	NS	----	0.035	NA
7	11	22.0	9	114	1.2	NS	----	0.118	NA
8	6	12.0	12	15.0	0.6	NS	0.029	----	PA
9	1	2.0	1	1.3	07	NS	---	0.007	NA
10	4	8.01	18	22.5	3.	0.025	0.151	---	PA
11	6	2.0	3	3.8	0.3	NS	---	0.077	NA
12	1	2.0	1	1.3	0.6	NS	NS	0.007	NA
13	1	2.0	2	2.5	1.0	NS	NS	NS	PA
14	2	4.0	2	1.3	0.3	NS	NS	NS	NA
52	2	4.0	1	1.3	0.3	NS	NS	NS	NA
53	2	4.0	3	3.8	0.8	NS	NS	NS	NA
BLANK	24		44						
TOTAL	100		160						

control revealed that DR10 was significantly (p=0.041) more frequent in NHL patients that HL patients (38 versus 22.5%) tables 3,4)

Table 2:

HLA-DR antigens	Healthy control no.50		HL-patients No.80		RR	P	EF	PF	Type of association
	N0.	%	N0.	%					
1	9	18.0	28	35.0	2.3	0.027	0.207	---	PA
2	11	22.0	15	18.8	0.8	NS	---	0.041	NA
3	14	28.0	18	22.5	0.7	NS	---	0.071	NA
4	9	26.0	13	16.3	0.5	0.027	---	0.115	NA
Blank	53		86						
Total	100		160						

Table 3: frequency of HLA –DR antigens in Hodgkin lymphoma patients and Non-Hodgkin lymphoma control.

HLA-DR antigens	Healthy control no.50		HL-patients No.80		P
	N0.	%	N0.	%	
1	3	6.0	9	11.3	
2	9	18.0	6	7.5	NS
3	13	26.0	29	36.3	NS
4	14	28.0	18	22.5	NS
5	2	4.0	2	2.5	NS
6	0	0.0	1	1.3	NS
7	2	4.0	9	11.4	NS
8	4	8.0	12	15.0	NS
9	1	2.0	1	1.3	NS
10	19	38.0	18	22.5	NS
11	4	8.0	3	3.8	0.044
12	1	2.0	1	1.3	NS
13	0	0.0	2	2.5	NS
14	2	4.0	1	1.3	NS
52	0	0.0	1	1.3	NS
53	3	6.0	3	3.8	NS
Blank	23		44		
Total	100		160		

Table 4: frequency of HLA –DR antigens in Hodgkin lymphoma patients and Non-Hodgkin lymphoma control

HLA-DR antigens	NHL control No.50		HL-patients No.80		P
	N0.	%	N0.	%	
1	18	36.0	28	35.o	NS
2	13	26.0	15	18.8	NS
3	8	16.0	18	22.5	NS
4	7	14.0	13	16.3	NS
Blank	54		86		
Total	10 0		16 0		

Discussion:

An association between HLA antigens and lymphomas was initially documented with class I antigens, later strongly arguments supporting the genetic linkage between susceptibility to lymphoma and HLA class II were reported and gave a clues about susceptibility or protection from the disease (Fog dell et al.,1998).

In the present study ,examination has done for 80 HL patients ,50 NHL patients control and 50 healthy control .the distribution and prevalence of HLA class II alleles are variance in different populations ,we have compared such alleles with control group .the result revealed that in patients with HL there were significantly increased frequency for certain alleles,DR3,DR10 and DQ1involed in HLA class II ,as compared to healthy control, which may confirm the existence of antigenic association between such alleles and the susceptibility to the HL in certain individuals.

DR10 allele most frequent in patient control, similer result were revealed by xixion et al., 1996). Who reported that DR10 alleles significantly increased .they also have suggested that HLA28, B18, B51,C4 and DQ4 alleles significantly increased as compared NHL patients with healthy control in 1994 Klitz et al ., reported in the NS subtype of HL,DRB1,DQA1, and DPB1 alleles significant increase this variation may reflect the differences observed in the prevalence of the disease due to different ethic group (Schroeder et al.,1998).

HLA type has been shown to modify risk of HL ,this explained by a signal of the HL-HLA relationship by race/ethnicity min which Oze et al .,(1994) found that HLA-DPB1 *0301 increased risk of HL in all ethnic groups, while HLA-DPB1*0401 was associated with a lowered risk of HL in Japanese and Chinese and an elevated risk for USA while races .thus ,HLA-DPB1*0401 or factors linked to it ,could explain some of the lower incidence of HL ,in certain Asian ethnic groups, although the opposing associations of HLA-DBP 10401 by race/ethnicity indicted that HL etiology is complex and involves environmental factors as well

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دور الضد لكريات الدم البيض نوع II البشري في المرضى العراقيين المصابين بسرطان هوجكن اللمفي

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الخلاصة:

لدراسة العلاقة بين ظهور مستضدات الخلايا البشرية النوع الثاني مع مرض سرطان الغدد اللمفاوية (الهوجكن) تم فحص (80) مريض مشخصين حديثا بهذا المرض ومجوعتين سيطرة وتشمل (50) مريض مشخص حديثا ومصابين بسرطان الغدد اللمفاوية (غير الهوجكن) و(50) شخص سليم غير مصابين وتم فحص مستضدات الخلايا البشرية البيضاء النوع الثاني لهم.

اظهرت النتائج وجود فرق معنوي في HLA-DR3 عند مرضى الهوجكن مقارنة بالاصحاء وتحت مستوى احتمال (PL0.01) وتحتوى مستوى احتمال(P>0.05) بالنسبة الل DQ1 . ولهذا نستنتج ان HLD-DR1وHLA–DQ3 لهما علاقة بظهور مرض الهوجكن عن العراقيين العرب.