Iraqi Journal of Cancer and Medical Genetics

The Association Between HLA-Class I Antigens and Polycystic Ovary Syndrome in a Sample of Iraqi Patients

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Abstract :

The association between HLA-class I (A and B) antigens and polycystic ovary syndrome was investigated in 45 Iraqi female patients during the period February - July 2010. Additionally, ABO blood group phenotypes (A, B, AB and O) were also investigated. The comparison was made with 40 apparently healthy females (controls) who were blood donors and matched patients for age and ethnicity. The O blood groups showed a significant (P = 0.02) decreased percentage frequency in patients as compared to controls (33.3 vs. 57.5%), but the corrected P (Pc) was not significant (Pc = 0.08). In contrast, the HLA antigens were presented with a corrected significant variation. The antigen HLA-B7 showed a significant (Pc = 0.016) increased percentage frequency in patients as compared to controls (42.2 vs. 10.0%), and such variation was associated with a relative risk (RR) value of 6.58 and an etiological fraction (EF) of 0.36. Such variation may highlight the importance of HLA system in conferring immunogenetic predisposition to develop ovarian cysts.

Key words: *Polycystic ovary syndrome (PCOS), HLA antigens, ABO blood groups.*

Introduction:

Polycystic ovary syndrome (PCOS) is a multifactorial, heterogeneous, complex genetic endocrine and metabolic disorder, diagno-stically characterized by chronic anovulation, polycystic ovaries and biochemical and clinical manifestations of hyperandrogenism.

It has a tremendous negative impact on the physiology and metabolism of the body as it may evolve into a metabolic syndrome with insulin resistance, hyperinsulinemia, abdominal obesity, hypertension and dyslipidemia presenting as frequent metabolic traits and culminating in serious long-term cones-quences, such as type 2 diabetes mellitus, endometrial hyperplasia and cardiovascular disease (1).

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The syndrome is detected in approximately 5-10% of women of repro-ductive age, and a recent evidence from experimental observations in animals suggest a deep-rooted development origin of PCOS, in which the pathophysiology may start from infancy to adulthood (2).

In utero fetal programming or dysregulation of the hypothalamic-pituitary-gonadotropic axis at crucial developmental stages, mediated by the interaction of genetically determined hyper-androgenism and environmental factors (obesity), may have a significant role in the development of the final expression of the PCOS phenotype and its long-term consequences (3).

Furthermore, familial aggregation of the disease is well established and there are ethnic and racial variations in the prevalence of the syndrome and its symptoms (4).

However, the etiology of PCOS remains unclear, but both genetic and environmental (particularly nutritional) factors are involved (5). One of these genetic factors is antigens of the major histocompatibility complex (MHC), which is known in human as HLA system. These antigens are genetically controlled by genes on the short arm of

chromosome 6, and their expression shows an extensive polymorphism (6).

These antigens and/or alleles have shown positive association with different diseases, including PCOS, and the presented evidences suggest that such system is involved in conferring an immunogenetic predisposition to develop these diseases (7, 8, 9).

Therefore, the present investigation came to shed light on the association between PCOS and two immunogenetic systems (ABO blood groups and HLA system) in a sample of Iraqi Arab patients.

Subjects, Materials and Methods:

Blood samples (8 ml) were collected in 10ml heparinized tubes from 45 female patients with PCOS, who were administrated to the AL-Karama Teaching Hospital (Baghdad) during the period February - July 2010. Their age range at the time of diagnosis was 17-45 years. The diagnosis was made by the consultant medical staff at the hospital, and based on clinical and ultrasonic examinations. A control sample of 40 apparently healthy females (blood donors) with an age range 19-35 was also included, and they matched patients for age and ethnicity (Iraq Arab Muslims).

The blood samples were first phenotyped for ABO blood groups (A, B, AB and O) using commercially available anti-sera (Biotest, Germany) by means of a slide agglutination test (10).

Then, the lymphocytes were isolated from the remaining blood by means of a density gradient centrifugation using lymphoprep as a separating medium. These lymphocytes were employed in the phenotyping of HLA-class I antigens (A and B) through the microlymphocytotoxicity test using commercially available anti-sera (Biotest, Germany) that recognized 8 HLA-A and 16 HLA-B antigens (11).

The data were statistically analyzed using the computer programme PEPI version 4.0. Significant differences between patients and controls were assessed by Fisher's exact probability (P), and the P was corrected (Pc) for the number of comparisons made for each system. A phenotype or antigen that showed a significant variation between patients and controls was also presented in terms of relative risk (RR), etiological fraction (EF) and preventive fraction (PF) (12).

Results:

The A, B and AB blood group phenotypes showed no significant variations between patients and controls, while blood group O showed a decreased percentage frequency in the patients (33.3 vs. 57.5%). Such variation was associated with a PF value of 0.36, and it was significant (P = 0.02) before the correction of P (Pc = 0.08) (Table 1).

Table 1: Observed numbers and percentage frequencies of ABO blood group phenotypes in ovarian cyst patients and controls.

ABO Phenotypes	Patients (No. = 45)		Controls (No. = 40)	
	No.	%	No.	%
A	16	35.6	9	22.5
B	7	15.6	5	12.5
AB	7	15.6	3	7.5
O*	15	33.3	23	57.5

** Blood group O: RR = 0.37, PF = 0.36, P = 0.02, Pc = 0.08 (Not significant)*

For HLA system, none of the eight HLA-A antigens showed a significant variation between patients and controls (Table 2). However, the HLA-B locus might have contradicted the theme, and out of 16 antigens tested, only HLA-B7 showed a significant (P = 0.001) increased percentage frequency in the patients (42.2 vs. 10.0%), and the difference maintained a significant corrected P (Pc = 0.016).

Furthermore, such variation was associated with RR value of 6.58 and EF value of 0.36 (Table 3).

Table 2: Observed numbers and percentage frequencies of HLA-A antigens in ovarian cystpatients and controls.

HLA-A Antigens*	Patients (No. = 45)		Controls (No. = 40)	
	No.	%	No.	%
A1	7	15.6	5	12.5
A2	20	44.4	14	35.0
A3	17	37.8	13	32.5
A9	11	24.4	10	25.0
A10	8	17.8	12	30.0
A11	3	6.7	3	7.5
A19	17	37.8	11	27.5
A28	1	2.2	2	5.0

**No significant difference between antigen frequencies of patients and controls.*

Table 3: Observed numbers and percentage frequencies of HLA-B antigens in ovarian cyst patients and controls.

HLA-B Antigens	Patients (No. = 45)		Controls (No. = 40)	
	No.	%	No.	%
B5	8	17.8	9	22.5
B7*	19	42.2	4	10.0
B8	0	0.0	4	10.0
B12	6	13.3	10	25.0
B13	1	2.2	4	10.0
B14	2	4.4	5	12.5
B15	1	2.2	3	7.5
B16	5	11.1	4	10.0
B17	4	8.9	4	10.0
B18	4	8.9	6	15.0
B21	4	8.9	8	20.0
B22	3	6.7	3	7.5
B27	0	0.0	3	7.5
B35	4	8.9	6	15.0
B40	5	11.1	6	15.0
B41	9	20.0	4	10.0

**HLA-B7: RR = 6.58, EF = 0.36, P = 0.001, Pc = 0.016 (Significant).*

Discussion:

The present study demonstrated that HLA-B7 was significantly increased in PCOS patients, and the antigen was four times more frequently observed in the patients than controls.

Such finding may highlight the importance of such marker in PCOS of Iraqi females. Such conclusion is strongly supported by the EF value, which was 0.36, and in a statistical interpretation the value may represent that 36% of the disease aetiology is due to such allele (12), and accordingly HLA-B7 may be considered as a predisposing immunogenetic marker for PCOS in Iraqi Arab populations. Inspecting HLA antigen frequencies in other world populations of PCOS revealed different observations. In Japanese patients, an increased frequency of HLA-B54 and HLA-Cw7 has been reported (13,14), while in Chinese patients; the disease was positively associated with HLA-B46.

Earlier studies in Caucasian PCOS patients were also

conflicting, but two studies suggested that HLA-B7 is positively associated with the disease (14,15).

The discrepancies between studies may be related to racial differences, because one of the hallmarks of HLA alleles is their different distributions in different populations around the world (6).

However, it is also possible to bridge the gap between these studies, especially if we notice that most of the observed associations were restricted to HLA-B locus.

Accordingly, such locus may harbor the PCOS predisposing gene but it is in linkage disequilibrium with different HLA-B alleles that are related to their frequencies in the world populations (15).

The other immunogenetic system that was investigated was ABO blood groups. This time, blood group O was decreased in PCOS patients and the associated PF value was 0.36.

However, no previous investigation that can confirm or contrast the present findings, but blood group antigens and/or alleles have been positively associated with ovarian tumours and other tumours (16,17).

A study in Russian ovarian tumour patients reported that AB blood group was significantly increased in the patients (18), while in other European caucasians, Rh positive patients had an increased risk to develop ovarian tumours or cysts, as compared to Rh negative patients (16,17). Further studies in this regard involved other blood group that was A in the formation of ovarian tumours and cysts (17,18,19). Again, such discrepancies may be related to racial differences between populations.

In conclusion, the HLA profile are important immunogenetic markers that may be related to the aetiopathogenesis of PCOS, but it is too early to reach a final conclusion about their roles and further investigations are required, especially if the detection of HLA alleles is based on a molecular methods.

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المصاحبة ما بين مستضدات خلايا الدم البيض البشرية – الصنف الاول ومتلازمة تعدد الاكياس المبيضية في عينة من المريضات العراقيات

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الخلاصة:

درست المصاحبة بين مستضدات خلايا الدم البيض البشرية-الصنف الاول (A وB) ومريضات مصابات بمتلازمة تعدد الاكياس المبيضية (45 انثى) للفترة شباط - تموز 2010. وبالاضافة الى ذلك درست الانماط المظهرية لمجاميع الدم (ABO), واجريت المقارنة مع 40 انثى صحيحة مظهريا (السيطرة) وهن من المتبرعات بالدم والمطابقات للمريضات من حيث العمر والانحدار العرقي. اظهرت النسبة المئوية لمجموعة الدم O انخفاضا معنويا (الاحتمالية = 0.02) في المرضى مقارنة بالسيطرة (33.3 مقابل 57.5%),.الا ان الاحتمالية المصححة (الاحتمالية المصححة = 0.08) كانت غير معنوية.

وبالمقابل اظهرت النسبة المئوية للمستضد HLA-B7 زيادة معنوية (الاحتمالية المصححة = 0.016) في المرضى عند المقارنة بالسيطرة (42.2 مقابل 10.0%), وقد تصاحبت هذه الزيادة بخطر نسبي مقداره 6.58 وعامل مسبب مقداره 0.36. تسلط هذه الفروقات الضوء على اهمية نظام مستضدات خلايا الدم البيض البشرية في الاستعداد الوراثي- المناعي لتطور مرض متلازمة تعدد الاكياس المبيضية في النساء العراقيات.