HLA ASSOCIATION WITH CHILDHOOD ACUTE LYMPHOBLASTIC LEUKEMIA

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Summary:

OBJECTIVE Many associations have been found between specific HLA antigens and increased susceptibility to various diseases. So we tried to associate class I and class II antigens with acute lymphoblastic leukemia. We also demonstrate the presence of antibodies in serum of acute lymphoblastic leukemic patients against HLA class I.

DESIGN: Prospective study.

SETTING: Tissue typing and histocompatibility center at Al-Karamah Teaching Hospital.

PATIENTS AND METHOD: 70 acute lymphoblastic leukemia patients from pediatric hospitals. HLA (human leukocyte antigens) typing done for them by serological method and cross matching and blood grouping were also done for them.

RESULTS: There was a significant difference between patients and control groups regarding HLA-A6, DR1, DR4, DR7, DQ1, DQ2, DQ3, DQ4. There was 42.6% (10/70) of patients had antibodies against HLA class I. There was no significant association between blood group and acute lymphoblastic leukemia.

CONCLUSION: Genetic factor increased susceptibility with acute lymphoblastic leukemia (HLA-DR1, DQ1, HLA-DR4, DQ4, HLA-DR4, DQ3, HLA-DR7, DQ2). This HLA typing increased susceptibility to be affected with leukemia after infection.

RECOMMENDATION: HLA typing was done to acute lymphoblastic leukemic patients by molecular-DNA based method (PCR-SSP, RSCA) in addition to serological method.

KEY WORD: ALL, HLA typing, antibodies, blood group.

Introduction

Leukemias are a group of malignant disorders of the hematopoietic tissues characteristically associated with increased numbers of primitive white cells (blasts) in the bone marrow. The cause of the leukemia is unknown in the majority of patients. Several factors are associated with development of leukemia like: ionizing radiation, cytotoxic drugs, retroviruses, immunological and genetic factors (1). Certain human diseases occur more frequently among individuals who carry particular MHC alleles. The main categories of diseases studied having a positive association with HLA antigens are those with a known or suspected hereditary factor (2) and those with a possible immunological basis (3). So we tried to investigate HLA class I and class II in children with acute lymphoblastic leukemia to detect the presence of antibodies directed against HLA class I and II antigens.

PATIENTS AND METHODS

- PATIENTS GROUP: Consist of seventy Iraqi Arab Muslims children patients complaining from acute lymphoblastic leukemia from pediatrics hospitals in first remission after treatment with traditional therapeutic regime. Lastly they were indicated for allogeneic bone marrow transplantation. Their age ranged from 5-11 years with median age (8 years). Fifty of them were male and the rest were female.

- CONTROL GROUP: Consist of 500 healthy control group, their age ranged from 3-45 years, median was 25 years. 355 of them were male and the rest was female.

HLA typing for class I and II, cross matches for detection antibodies in their serum were done by complement dependent lymphocytotoxicity test (4). Blood group were also done for them. Statistical analysis was done by using Chi-square test.
RESULTS:
Acute lymphoblastic leukemia were more common in male children. Their phenotype and 
gene frequency in those patients were shown in table -1-. there was no significant difference between patients group and control group in the 
following HLA antigens : A2, A3, A11, A24, A26, 
A33, B7, B8, B18, B41, B44, B53, B38, B37, B39, 
B53, B60, B63, C3, C4, C7, DR52, DR53, DR2, 
DR3, DR5, DR6, DR10. In addition, there was 
significant difference in the following antigens : 
(Cw6, DR4, DR1, DR7, DQ1,DQ2,DQ3,DQ4) 
table -1-. Relative risks were equal one or more or 
less than one in different antigens table-1A-. The 
percentage of acute lymphoblastic leukemic 
patients who had antibodies in their serum against 
HLA antigens class I (positive cross- matches) was 
(14.2%) table-2-. Their was no significant 
difference between patients and control regarding 
blood groups as shown in the table -3-.

DISCUSSION:
It had been suggested that childhood leukemia 
may be the abnormal outcome of a common 
infestation. Rare events caused by a common 
environmental events such as infestation are likely to 
be influenced by host genetic susceptibility (5). We 
have therefore investigate whether immunogenetic 
(HLA typing ) susceptibility contribute to the risk 
of childhood acute lymphoblastic leukemia . In this 
preliminary study we report that children with acute 
lymphoblastic leukemia carry the following HLA 
locus alleles: HLA-Cw6, DR1, DR4, DR7, DQ1, 
DQ2, DQ3, DQ4 with significant difference than the 
control group , their relative risks were 3 , 2 , 
1.7, 7.1, 3.2, 9.2, 10.1, 3.5 and 0.2 respectively. 
Moreover, there is a linkage disequilibrium between 
(DR1 DQ1, DR7 DQ2, DR4 DQ3 and DR4 DQ4 ) 
which is in agreement with other results (6). These 
results suggest that HLA - C , HLA- DR and HLA- 
DQ either alone or with other alleles contribute to 
the risk of childhood acute lymphoblastic leukemia 
possibly by increasing susceptibility to an 
infectious agent (5).Other studies showed that HLA 
- DPB1* 0201/ *0301/0401 and / * 0402 were 
more frequent in patients with acute lymphoblastic 
leukemia (ALL)(5).

A molecular analysis was carried in ALL 
patients to investigate the heterozygosity for HLA-
DR53 and were not different between patients and 
control (7). It is in agreement with our results 
regarding HLA- DR 53 and DR52. Molecular 
mimicry of an HLA-DR 53 epitope by oncogenic re'to 
viruses or susceptibility genes in linkage 
disequilibrium with HLA-DR 53 may be 
responsible for this association (7).

It had been found that DR4 and DQ2 were 
significantly correlated with acute myeloid 
leukemia with favorable remission rates and 
s survival (8). While in our study we showed that 
HLA-DR4 and DQ2 are significantly correlate with 
ALL. Possible mechanisms for this association 
include the linkage or co- inheritance of an 
occugen, facilitate the binding of a transforming 
virus , toxin, cytokine and impaired 
imunerecognition of an emerging neoplas (8).

Other HLA antigen that were detected included 
HLA - B38 which is present in 10-20 % of the 
Jewish population and is associated with T- 
cell leukemia (9) and HLA-B35 increased in Ashkenazi 
Jews of European origin with chronic 
lymphoblastic leukemia (10). While in our study 
HLA- DR35 and B38 , there were no significant 
differences between patients and control probably 
due to racial factors. We only studied Arab 
Muslims.

Family studies showed that Cw3 and Cw4 
may be markers for leukemia susceptibility genes 
(17). This observations imply that in leukemia 
families unknown MHC - linked recessive factors 
linked to Cw3 and Cw4 alleles may be due to 
susceptibility genes which also cause segregation 
distortion of HLA genes and probably development 
al errors (17). In our study , we only analyzed ALL 
and we only studied patients and not whole family 
because of shortage of materials and cost. We found 
that only Cw6 had significant difference between 
patients and control. In the future we will do family 
study.

The frequencies of HLA-DRB1*0403, *0802, 
*1403 and *1405 were significantly higher in 
Japanese patients with chronic myelogenous 
leukemia (11). Our results showed that HLA -DR4 
had significant difference in patients with ALL.

DNA typing of HLA- alleles in CLL patients 
showed that increased frequencies of HLA-DRB4 
* 0103, DRB1* 0401, DQB1 * 0302 and HLA - 
DPB1* 0301 in patients with CLL (12). Our data 
showed that DR4 and DQ3 had significant 
association with ALL. This suggest that factors 
within or close to the human MHC class II regions 
confer susceptibility to CLL (12).

Other results found that male patients had a 
higher frequencies of DQA * 0101 / *0104 and 
DQB1 * 0501 than control group in ALL . this 
results suggest a male associated susceptibility 
haplotype in ALL and supports an infectious 
etiology (13).This is in agreement with our results 
that there was significant association and increase 
in HLA-DQ1 in male patients with ALL.

Our data showed no significant increase in 
antibodies in serum patients .Other studies showed 
decrease in these antibodies due to using leukocyte 
depleted blood (14).

Lastly there was no association between 
blood group and ALL.

This difference in results may be due to 
racial factors , religion, method we used 
(serological) while all studies used molecular DNA
based method (PCR-SSP, RSCA) which is more accurate and sensitive (15,16).

REFERENCES:


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<th>HLA antigens</th>
<th>Patient No.</th>
<th>Patient phenotype</th>
<th>Patient gene frequency</th>
<th>Control No.</th>
<th>Control phenotype</th>
<th>Control Gene frequency</th>
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<th>P-value</th>
<th>(Odd ratio) Relative risk</th>
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<td>0.1</td>
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<td>N.S.</td>
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<td>0.1</td>
<td>90</td>
<td>0.1</td>
<td>0.1</td>
<td>6.7</td>
<td>P&lt;0.01</td>
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<td>0.1</td>
<td>0.1</td>
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<td>60</td>
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<td>6.8</td>
<td>P&lt;0.005</td>
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</table>

Table 1- HLA phenotype and gene frequency in patients with acute lymphoblastic leukemia and controls showing Chi-square, P-values and odd ratios. (N.S. = not significant)
Table-2- the number and percentages of acute lymphoblastic leukemia patients with positive antibodies against HLA class I antigens.

<table>
<thead>
<tr>
<th>Cor. rol N°.</th>
<th>Patients with positive cross matches No. %</th>
<th>Patients with negative cross matches No. %</th>
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<tbody>
<tr>
<td></td>
<td>10 14.2</td>
<td>60 85.7</td>
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</table>

Table -3- the number and percentages of acute lymphoblastic leukemia with different blood groups compared with healthy normal control group.

<table>
<thead>
<tr>
<th>Blood groups</th>
<th>Patients No. %</th>
<th>Control No. %</th>
<th>Chi square</th>
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<td>O</td>
<td>28 40</td>
<td>195 39</td>
<td>0.001</td>
<td>N.S.</td>
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<tr>
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<td>145 29</td>
<td>0.1</td>
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</tr>
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<td>6 8.5</td>
<td>25 5</td>
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N.S. = not significant