

RELATIONSHIP BETWEEN ABO AND RH BLOOD GROUPS WITH CHILDHOOD ACUTE LEUKEMIAS AND LYMPHOMAS

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ABSTRACT

Background: After demonstrating the relationship between blood types and stomach cancer, it was suggested that there may be a relationship between blood groups and other cancers. There are few studies on the relationship between hematological malignancies and blood groups, and these studies yielded different and conflicting results. **Objectives:** The aim of this study was to identify any association between ABO and Rh blood groups with childhood acute leukemias and lymphomas and their outcome. If there is a relationship, it may be used as a marker for epidemiology and prognosis of acute leukemias and lymphomas. **Methods:** This is a hospital based retrospective study, conducted between January 1991 and December 2006. Total 986 patients' records, whom were below the age of 16 years with newly diagnosed acute leukemias and lymphomas were reviewed. ABO and Rh blood groups distributions of patients diagnosed with acute leukemias and lymphomas were compared with ABO and Rh blood group distribution of healthy people in Turkey. **Results:** In this study, 986 patients under 16 years of age were included. Of 986 cases of malignancies, the most common was Acute Lymphoblastic Leukemia (ALL) (44.3%), Hodgkin Lymphoma (HL) (19.9%), Acute Myeloid Leukemia (AML) (16.1%), Non-Hodgkin Lymphoma (NHL) (13.8%), and the least Burkitt Lymphoma (BL) (5.9%). The distribution of blood grouping showed that, mainly of cases were of blood Group A (43.2%), followed by O (32.4%), B (17.3%), and AB (7.1%). Majority of cases were Rh positive (90.6%). We found that only Rh (+) blood group in AML was statistically significantly higher than other groups and general in Turkey. **Conclusions:** This study demonstrated that larger-scale clinical studies are needed to use blood group antigens as long-term follow-up and prognosis indicators in AML, also more studies at the molecular level. In addition, the studies examining the relationship between transferase enzymes and carcinogenesis are required for the formation of A antigen and B antigen.

KEYWORDS: Childhood Acute Leukemia; ABO and Rh blood groups; Childhood Lymphoma.

BACKGROUND

Acute Leukemias and lymphomas are the most common malignancies of childhood in the most countries of the world. The etiology of childhood leukemias and lymphomas are multifactorial. The exact cause is still unknown, but several environmental, genetic, viral and immunological factors may contribute to the evolution of these diseases.^[1] However, the association between blood groups and these malignancies are not well established.

ABO antigens are considered as red blood cell antigens, but also they are expressed on a variety of human tissues and are found on the most endothelial and epithelial cells, and are present in all body fluids except cerebrospinal fluid. It is known that blood group antigens participate in cell recognition and cell adhesion from their specific properties. Accordingly, it is likely to play a role in the formation of tumors, metastases, and

prognoses. There are a few well-known associations between ABO blood types and certain malignancies. It has been found that gastric carcinoma is mostly seen in people with blood type A, also duodenal ulcers are more common in people with blood type O.^[2-4] Additionally, the studies have suggested that ABO blood groups can be used as an epidemiological marker or a primary screening tool to define populations at high risk for specific hematological malignancies.^[2]

OBJECTIVES

As a result, blood groups could be used as an epidemiological marker to determine the high-risk population, in case the risk of these malignancies are known, for the different ABO blood groups. Several studies have reported contradictory results about the relationship between ABO blood groups and acute leukemia.^[2,5-8] There are very few studies on this subject

in pediatric patients. Therefore, we wanted to determine the distribution of ABO blood groups among children with acute leukemias and lymphomas and compare them with the distribution of ABO and Rh blood groups in Turkey.

METHODS

The study was carried out in the pediatric oncology clinic of Sami Ulus Children's health and diseases hospital. The data were collected from the case records of patients who were admitted to the hospital between January 1991 and December 2006. Total 986 patients under 16 years of age with newly diagnosed Acute Lymphoblastic Leukemia (ALL), Acute Myeloid Leukemia (AML), Hodgkin Lymphoma (HL), Non-Hodgkin Lymphoma (NHL) and Burkitt Lymphoma (BL) were included. Age, gender, residence, date of diagnosis, blood type, white blood cell count value, hemoglobin value, areas of involvement, histopathological diagnosis, stage, risk group, final clinical condition, presence of relapse and relapse sites were included in the study. Patients were divided into 5 groups according to their malignancy diagnosis. The first group was ALL, the second group was ANLL, the third group was NHL, the fourth group was HL, and the fifth group was patients with BL. ABO and Rh blood groups distributions of patients diagnosed with acute leukemias and lymphoma were compared with the ABO and Rh blood group distribution of healthy people in Turkey and the characteristics of patients in both groups. The blood group distribution of our blood center was not used, because only ill children come to our hospital. For blood group distribution in Turkey, the study of Ergun et al named "The distribution of ABO blood group and Rh factor overall in Turkey" was used.^[9]

In our hospital, after the diagnosis of malignancy, blood groups of all patients were determined in terms of urgent blood needs. These results were examined from the files. In our hospital, ABO and Rh blood groups were evaluated using the tube method between 1991-2004, Sanquin microplate method between 2004-2006 and Diamed microtyping system for 2006.

The diagnosis of acute leukemia and its subdivision was made as a result of the morphological, histochemical and immunophenotypic evaluation of the bone marrow aspiration and biopsy by routine methods. The morphological typing of blasts was made according to the French-American-British (FAB) sub-classification. The diagnosis of lymphoma was made by the histopathological examination and immunohistochemical staining of the tissue.

The study was approved by the Ethics Committee of Sami Ulus Children's health and diseases hospital with number 01271 on 16.06.2006 and was conducted according to the principles of the Declaration of Helsinki.

Statistical analysis

The statistical analysis was performed using SPSS for windows version 16.0 software. (11.5). The results are given as mean \pm 1 standard deviation ($\bar{x} \pm SD$). The overall distribution of blood groups in ALL, AML, HL, NHL, BL and control groups were compared using the chi-squared test. In the comparisons of the groups within and between groups, the chi-squared test, Fisher's exact test and one-way analysis of variance test ANOVA were used. In addition, relationships between parameters were analyzed using correlation analysis. The 95% confidence intervals (95% CI) were calculated using binomial distribution probability. The p value of less than 0.05 was considered as statistically significant.

RESULTS

A total of 986 patients with diagnosis of 437 ALL, 19 AML, 136 NHL, 196 HL and 58 BL who were followed up in the pediatric oncology clinic between January 1991 and December 2006 were included in the study.

The mean age was 6.95 ± 3.8 years for ALL; 7.87 ± 3.8 years for AML; 7.85 ± 3.6 years for NHL; 8.72 ± 3.52 years for HL and 5.93 ± 2.65 years for BL. Mean ages were significantly different between the groups. The mean age of the ALL and BL groups were found to be significantly lower than the mean values of the other three groups ($F=11,16$ $p<0,001$).

The Male:Female ratio of 1.52 for ALL; 1.17 for AML; 3.25 for NHL; 2.84 for HL and 2.41 for BL. The gender distributions of the groups were statistically different. The number of male patients in the ALL and AML groups was found to be statistically lower than the other three groups ($\chi^2=27,9$, $p<0,001$).

ABO and Rh blood group distributions of the patient groups and general in Turkey are shown in the table 1. No statistically difference was found in terms of ABO blood group distributions of patient groups and general in Turkey (for each comparison $p>0,05$). No statistically difference was found in terms of Rh blood group distributions of ALL, NHL, HL, BL groups and general in Turkey (for each comparison $p>0,05$). But Rh (+) blood group in AML was statistically significantly higher than other groups and general in Turkey ($p<0,05$).

ABO and Rh blood groups of the ALL patients were compared with the patients' cell subtypes (T, B, T+B, Calla + B), blastic cell types according to FAB classification (L1, L2, L3), risk group (standard, high), presence of relaps and the final clinical status (remission, ex). No statistically relationship was found between both blood groups and these features in ALL.

ABO and Rh blood groups of the AML patients were compared with the patients' blastic cell types according to FAB classification (M0, M1, M2, M3, M4, M5, M7), risk group (standard, high), CNS involvement at the time of diagnosis, presence of relaps and the final clinical

status (remission, ex). While M2 subtype was found more in AML patients with B blood group (31%), M4 subtype was found more in AML patients with O, A and AB blood group. Additionally, M3 subtype was found more in AML patients with Rh(-) blood group (55.6%). High risk was found to be less in AML patients with AB blood group (30%). CNS involvement at the time of diagnosis was observed only in patients with O, A and Rh(+) blood groups, respectively 3.8%, 3% and 2.7%. The presence of relapse was observed more frequently in AML patients with AB blood group (50%). However statistically correlation was not found between both blood groups and these features due to insufficient number of cases in AML ($p>0,05$).

ABO and Rh blood groups of the NHL patients were compared with the patients' cell subtypes (T, B), primary involvement region (subdiaphragmatic, supradiaphragmatic, both), histopathological type (lymphoblastic lymphoma-LBL, large cell lymphoma-LCL), stage (early, advanced), CNS involvement at the time of diagnosis, presence of relaps and the final clinical status (remission, ex). T cell subtype was not detected in any of the patients with B blood group. Subdiaphragmatic involvement was found more in NHL patients with O blood group (50%). LCL was less in AB blood group (37.5%), while it was higher in Rh(-) blood group (69.2%). Advanced stage was seen more in B blood group (52.6%). CNS involvement at the time of diagnosis was not detected in any of the NHL patients with AB blood group. While relapse was more seen in AB blood group (20%), no relapse was observed in A blood group (0%). Deaths were less in patients with B

and Rh(+) blood groups (6.3% and 10.7%). Yet statistically correlation was not found between both blood groups and these features due to insufficient number of cases in NHL ($p>0,05$).

ABO and Rh blood groups of the HL patients were compared with the patients' cell subtypes (lymphocyte predominance-LP, mixed cellular-MC, lymphocyte depleted-LD, nodular sclerosing-NS), stage (early, advanced), presence of B symptoms, presence of relaps and the final clinical status (remission, ex). While LP cell subtype was more seen in AB blood group (20%), LD cell subtype was more found in Rh (-) blood group (18.2%). No relapse was observed in AB and Rh(-) blood groups. No deaths was seen in Rh(-) blood group. However statistically correlation was not found between both blood groups and these features due to insufficient number of cases in HL ($p>0,05$).

ABO and Rh blood groups of the HL patients were compared with the patients' primary involvement region (subdiaphragmatic, supradiaphragmatic, both), stage (early, advanced), presence of relaps and the final clinical status (remission, ex). Only subdiaphragmatic involvement was detected in patients with the Rh (-) blood group. All patients with B, AB and Rh(-) blood groups were in advanced stage. No relapse was observed in A, AB and Rh(-) blood groups. No deaths was seen in B, AB and Rh(-) blood groups. Yet statistically correlation was not found between both blood groups and these features due to insufficient number of cases in BL ($p>0,05$).

Table 1: ABO and Rh blood group distributions of patient groups and populations of Turkey.

| Blood Group | ALL** | | AML** | | NHL** | | HL** | | BL** | | Turkey* | |
|--------------|-------|------|-------|------|-------|------|------|------|------|------|---------|-------|
| | n | % | n | % | n | % | n | % | n | % | n | % |
| O | 142 | 32.5 | 53 | 33.3 | 43 | 31.6 | 64 | 32.7 | 17 | 29.3 | 92992 | 32.24 |
| A | 191 | 43.7 | 67 | 42.1 | 64 | 47.1 | 80 | 40.8 | 24 | 41.4 | 128723 | 44.62 |
| B | 74 | 16.9 | 29 | 18.2 | 19 | 14.0 | 37 | 18.9 | 12 | 20.7 | 44571 | 15.45 |
| AB | 30 | 6.9 | 10 | 6.3 | 10 | 7.4 | 15 | 7.7 | 5 | 8.6 | 22183 | 7.69 |
| Rh(-) | 43 | 9.8 | 9 | 5.7 | 14 | 10.3 | 22 | 11.2 | 4 | 6.9 | 34236 | 11.87 |
| Rh(+) | 394 | 90.2 | 150 | 94.3 | 122 | 89.7 | 174 | 88.8 | 54 | 93.1 | 254233 | 88.13 |
| Total | 437 | 100 | 159 | 100 | 136 | 100 | 196 | 100 | 58 | 100 | 288469 | 100 |

Comparison with Turkey population for ABO blood group $\chi^2=1.38$ and $p>0,05$. Comparison between groups for ABO blood group $\chi^2=3.19$ and $p>0,05$. Comparison with Turkey population for Rh blood group $\chi^2=0.87$ and $p>0,05$. Comparison between groups for Rh blood group $\chi^2=1.94$ and $p>0,05$. Comparison between AML and Turkey population for Rh blood group $\chi^2=5.86$ and $p<0,05$. Comparison between AML and other groups for Rh blood group $\chi^2=5.92$ and $p<0,05$.

DISCUSSION

While neoplastic diseases are the second reason of the child death causes in developed countries, it is the fourth

in our country. So trying to prevent cancer by revealing the predisposing factors that determine the etiology and prognosis of the diseases is important. In this study, the role of ABO and Rh blood groups on prognosis and epidemiology of childhood acute leukemia and lymphomas were tried to be revealed. There are few studies in the literature investigating the relationship between cancer and blood group in childhood.

Since their discovery, ABO and Rh antigens are considered as red blood cell antigens and have been used only for blood transfusion, organ donation and research purposes. But also they are expressed on a variety of human tissues and are found on the most endothelial and

epithelial cells, and are present in all body fluids except cerebrospinal fluid.^[10]

Additionally, it is known that blood group antigens participate in cell recognition and cell adhesion from their specific properties. For example; LW antigen (Rh antigen) is known as the intracellular adhesion molecule (ICAM-4). Also CD44 (lymphocyte homing receptor), another adhesion molecule, plays a role in lymphocyte (T cell) activation, hematopoietic development and tumor metastasis. CD44 was found to be identical to the blood group antigen Inb. Additionally, T and Tn blood group antigens are used in cancer diagnosis and immunotherapy trials. Furthermore, some Lewis antigens (eg Lex) are thought to appear on malignant cells and are crucial for the malignant cell to metastasize.^[11] Accordingly, it is likely to play a role in the formation of tumors, metastases, and prognoses.

ABO and Rh blood group profiles among countries show great differences depending on ethnicity and race. However, in most of the studies, the most common blood type O in Mexico, Nigeria, Iraq also the most common blood type is A in Latin countries and the least blood type is AB in worldwide.^[12] The blood group distribution rate in Turkey is similar to the blood group distribution rate in Europe, the Caucasus, Cyprus and Lebanon, and higher incidence of A blood group seen in Turkey.^[13] We used data from Ergun's study for the distribution of blood group of healthy individuals in Turkey.^[9]

After Aird et al showed the relationship between blood type and gastric cancer in 1953, many studies were conducted to show the relationship between various malignancies and blood groups. For example, the frequency of A blood group in gastric cancer and the frequency of O blood group in duodenal cancer were found to be increased.^[14] The studies investigating the relationship between hematological cancers and ABO blood group distribution were back to 1960. However, contradictory results were obtained in previous studies, since blood group distributions were examined without dividing cancers into subgroups. In the last 20 years, cancers have been divided into subgroups and investigated again, but the relationship between childhood leukemia and lymphomas and blood groups has not been studied much. Additionally, it is still a matter of debate.

ABO system is formed by oligosaccharide chains which is a terminal sugar attached to a carbohydrate chain on membrane glycosphingolipids. O type is amorphous of the ABO blood group system. There is only H antigen on erythrocyte membrane in O group. H antigen is the precursor molecule for A and B antigens. Transferases add N -acetyl galactosamine or galactose to the H antigen for the A or B antigens, respectively.^[15] It is common to see decreased A and B antigens in patients with acute leukemia. It is thought to be the result of defect in glycosyl transferase enzymes in leukemia.^[16]

They showed that the methylation of ABO promoter in AML patients were higher than other leukemias and control group. Shao et al suggested that ABO promoter methylation level was a free predictive factor and closely related to development and prognosis of leukemia and MDS.^[18]

In previous studies, the loss of ABO antigens from the surface of red blood cells has been observed in patients with hematological malignancies. This loss of antigen may occur as a result of a predisposing factor to acute leukemia, a secondary effect to acute leukemia, or simply an association.^[16,19,20]

Different results were obtained due to the fact that the studies on this subject in the literature included a small number of patients, the use of blood donors as controls, and ethnic and geographical differences.

In the study of Iodice et al, A blood group was found more frequently in patients with ALL and O blood group in patients with HL and NHL, but there was no statistically significant difference.^[14] Tavasolian et al showed that patients with ALL had a higher rate of AB blood type.^[21] Afrose et al showed that there is a strong association between type O blood and AML.^[22] Both Ali H. Ad'hiah and Novaretti found that the most common blood type was "O" in acute leukemia patients.^[5,23]

There are also studies in the literature that obtained different results according to gender. Both Mustacchi and Nagy et al reported that the rate of O blood group increased in female patients with acute leukemia.^[24,25] However, in a study by Ravarian et al, B blood group was found more frequently in female patients with acute leukemia, but it was not statistically significant.^[26] In the Jackson study, while O blood type was decreased in female patients with acute leukaemias, acute leukemia was more often seen in males with O blood group and females with B blood group, in Northeast Malaysia. However, when divided into 2 subgroups as ALL and AML, a statistically significant result could not be obtained.^[27] In our study, no relationship was found between blood groups according to gender.

When we look at the studies from Turkey, they were made in adults except ours. Nevruz and colleagues from Turkey could not be demonstrated a significant difference in the distribution of ABO between ALL and AML patients.^[28] Fatih Kar et al found that although A Rh(+) blood group rate was higher in ALL and AML than other leukemias, there was not statistically significant results, due to the small number of patients.^[29] In the study conducted by Bascı S et al, although the frequency of blood group A was found to be higher in ALL patients, this finding was not statistically significant when compared with healthy individuals.^[30] In the study of Sahin D et al, no relationship was found between ABO and Rh blood groups in patients with AML.^[31]

When we look at the studies on children, there are few studies in the literature and the relationship is not clear. Ochoa-Garcia et al's study demonstrated that AB blood group was more seen in all AML patients. Also in the same study, B blood type was seen more and AB blood type was seen very little in pediatric ALL group.^[12]

Samin Alavi et al determined in children that there is an increased proportion of O and A blood group in ALL and AML, respectively. Statistically, O blood group had an increased rate in ALL, and they argued that the loss of ABO antigens may be associated with an increased risk of ALL. Samin alavi et al showed that statistically B and O blood groups are increased in Hodgkin's lymphoma and ALL, respectively. They also showed that A blood group was less frequent in HL and NHL. Also their study is the first done in children and the first study to examine the relationship between AML and ALL and ABO blood groups separately. They concluded that the loss of ABO antigens is unacceptable as an explanation for the increase in the O blood group ratio in ALL, because it is observed mainly in AML.^[15] Sakic et al determined that A and O blood types have a higher incidence in children with AML and ALL, respectively. They found that the distribution of ABO blood groups were important in children with acute leukemia.^[32] Also among children with ALL and the general population, the main and the least recorded types were O Rh(+) and AB Rh(-), respectively in Hasanein H. Ghali et al study.^[33] Also when leukemia is viewed without subgrouping, Steinberg reported that the distribution of ABO blood groups in children with acute leukemia were similar to the general population.^[8]

Safaa et al demonstrated that blood type O Rh (-) was found associated with poor prognosis, while A Rh (+) was seen more with favorable prognosis in AML.^[34] MacMahon and Forman could not find a relationship between the ABO blood group and the survival of the patients with acute leukemia.^[35] In parallel with the literature, we couldn't find a relationship between the survival and the blood groups.

In the literature; the studies showed that AB or A blood type increases in AML. However, there is no study about relationship between Rh blood group and AML in children. We only found that Rh (+) blood group in AML was statistically significantly higher than other groups and general in Turkey. Conflicting results of previous studies, this study suggests that there may be a relationship between Rh and AML, but our data are collected from a single hospital and we have a small number of patients, so a prospective study with a large population is needed.

CONCLUSION

According to these results, we think that ABO and Rh blood group antigens may play an important role in AML pathogenesis and prognosis. This study demonstrated that larger-scale clinical studies are needed to use blood

group antigens as long-term follow-up and prognosis indicators in AML. However, it should be kept in mind that ABO / Rh phenotypes may also change according to racial and geographical differences. In conclusion, studies with blood groups should continue in order to understand the place of blood groups in the etiology of hematological malignancies and to understand whether they can be used as an epidemiological marker.

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