Haptoglobin phenotypes in Brazilian patients with leukemia

Paulo Vidal Campregher; Irene Lorand-Metze; Helena Zerlotti Wolf Grotto; Maria de Fatima Sonati

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abstract

Haptoglobin (HP) phenotypes were determined in 188 Brazilian patients with the four most common types of leukemia: acute myeloid leukemia (AML), chronic myeloid leukemia (CML), acute lymphoblastic leukemia (ALL) and chronic lymphocytic leukemia (CLL), and were compared to 197 normal controls. We could not confirm the previously suggested increased incidence of the HP1 gene and the HP1-1 phenotype among leukemic patients. A higher frequency of haptoglobinemics (HP0) was observed among patients, in agreement with previous findings.

Introduction

Haptoglobin (HP) is a hemoglobin binding α2-globulin fraction of the serum with antioxidant and immunomodulatory properties (9, 14, 15, 18, 21, 24). In humans, HP is characterized by a genetic polymorphism of the α-chain, with three major phenotypes: HP1-1, HP2-2 and HP2-1, which are the expression of two alleles (HP1 and HP2) on chromosome 16q22.1 (40).

Several authors have evaluated the correlation between HP types and different diseases, such as neoplasias, chronic pathologies, diabetes, hypercholesterolemia, cardiovascular diseases, etc. (1, 4, 8, 12, 13, 19, 25). The significance of this polymorphism in leukemias has also been investigated, with controversial results, suggesting an association of the HP1 gene and the HP1-1 phenotype with AML, CML and ALL (7, 16, 17). In order to contribute to this matter, we determined the HP phenotypes of 188 Brazilian patients with leukemia.

Material and methods

Serum samples were obtained from 223 adult patients with leukemia, treated either at the UNICAMP University Hospital, in Campinas, or at the São Paulo Hematology Center, in São Paulo, both in the state of São Paulo.
São Paulo, Southeast Brazil. Patients were classified into the four main groups: AML (n = 42), CML (n = 78), ALL (n = 20) and CLL (n = 48). Diagnosis and classification were based on the morphologic characteristics of the peripheral blood and bone marrow cells, associated with leukocyte cytochemistry and immunophenotyping. A control group (CG) was composed of 210 blood donors from the same geographical region, 104 Caucasians and 106 African descendants. Thirty-five patients (15.7%) and 13 controls (6.2%) did not present detectable levels of Hp, evaluated by electrophoresis on cellulose acetate, and were considered haptoglobinemic (designated as Hp0). They were omitted from the calculation.

HP types were determined by acidic urea polyacrylamide gel electrophoresis. The patient groups were compared with the controls by using χ² test for gene frequency distribution. The Caucasian and African descendant blood donor subgroups were previously compared and did not significantly differ with respect to the HP gene frequencies (p = 0.994) and HP phenotype distribution (p = 0.227), being kept as a unique control group.

Results

The HP phenotypes and HP gene frequencies found in the patients and in the CG are demonstrated in Table 1, while the results of the comparisons between each leukemic group and the controls are summarized in Table 2. We could not find any significant difference in any of these comparisons.

Discussion

Haptoglobin, beside the hemoglobin binding function, is an acute-phase reactant protein; its antioxidant and immunomodulatory properties have been extensively investigated. It has recently been demonstrated that different HP phenotypes show distinct antioxidant activities and that the HP 2-2 phenotype is a less effective protector than HP1-1 [10, 14]. The latter corresponds to a small and dimeric protein, while 2-1 is a linear polymer with intermediate dimension and 2-2 is a large cyclic polymer. These characteristics are important determinants of the biological activities of each HP subtype [16]. In diabetes, for instance, HP has been focused as one major genetic factor involved in the susceptibility to coronary artery disease. In cancer, this correlation is not so clear. Awadallah and Atoum, investigating patients with breast cancer, found that the family history plays a relevant role in determining the degree of association between the disease and HP polymorphism. In leukemias, a recent study using microarray technology to analyze gene expression in CML cells demonstrated that the HP gene is one of the up-regulated genes. The authors, however, did not compare different HP genotypes. So, their influence on the mechanisms of defense or susceptibility to disease remains inconclusive, meaning that far more studies are necessary to clear up the relation of HP subtypes and leukemias.

Table 1

<table>
<thead>
<tr>
<th></th>
<th>Hp 2-2</th>
<th>Hp 2-1</th>
<th>Hp 1-1</th>
<th>n (total)</th>
<th>Hp 2</th>
<th>Hp 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>CG</td>
<td>44 (22.3%)</td>
<td>108 (54.8%)</td>
<td>45 (22.9%)</td>
<td>197</td>
<td>0.498</td>
<td>0.502</td>
</tr>
<tr>
<td>AML</td>
<td>13 (31%)</td>
<td>24 (57.1%)</td>
<td>5 (11.9%)</td>
<td>42</td>
<td>0.595</td>
<td>0.405</td>
</tr>
<tr>
<td>CML</td>
<td>23 (29.5%)</td>
<td>42 (53.8%)</td>
<td>13 (16.7%)</td>
<td>78</td>
<td>0.564</td>
<td>0.416</td>
</tr>
<tr>
<td>ALL</td>
<td>3 (15%)</td>
<td>13 (65%)</td>
<td>4 (20%)</td>
<td>20</td>
<td>0.475</td>
<td>0.525</td>
</tr>
<tr>
<td>CLL</td>
<td>18 (37.5%)</td>
<td>22 (45.8%)</td>
<td>8 (16.7%)</td>
<td>48</td>
<td>0.604</td>
<td>0.396</td>
</tr>
</tbody>
</table>

Conclusion

The previously reported high incidence of the HP1 gene and the HP1-1 phenotype among patients with AML, CML and ALL could not be confirmed in this study, since no significant differences were found in the comparisons. On the contrary, here the patients with CLL showed the highest incidence of the HP2 gene (0.604), with a p value tending towards significance (p = 0.061).

The previously reported high incidence of undetectable HP in leukemia patients was confirmed in this study (p = 0.002). The HP0 phenotype may be primarily due either to deletions that remove the HP genes or to point mutations that inactivate them. These data must be carefully evaluated, however, because patients with leukemia often...
Table 2

<table>
<thead>
<tr>
<th></th>
<th>$\chi^2$ (1)</th>
<th>$p$</th>
</tr>
</thead>
<tbody>
<tr>
<td>AML x CG</td>
<td>2.650</td>
<td>0.104</td>
</tr>
<tr>
<td>CML x CG</td>
<td>1.987</td>
<td>0.159</td>
</tr>
<tr>
<td>ALL x CG</td>
<td>0.073</td>
<td>0.787</td>
</tr>
<tr>
<td>CLL x CG</td>
<td>3.520</td>
<td>0.061</td>
</tr>
</tbody>
</table>

have associated conditions that can reduce the plasmatic HP levels, such as hemolysis or hepatic disease.

Acknowledgments

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References


Maia de Fátima Sonati
Departamento de Patologia Clínica da FCM/UNICAMP
Caixa Postal 6111
CP 13033-970 – Campinas-SP
Tel.: (19) 3788-9451
Fax: (19) 3788-9434
e-mail: sonati@fcm.unicamp.br