Letter to the Editor

Hereditary spherocytosis and the (TA)nTAA polymorphism of UGT1A1 gene promoter region—A comparison of the bilirubin plasmatic levels in the different clinical forms

To the editor,

Hereditary spherocytosis (HS) is the most common non-immune hemolytic anemia in individuals of northern European ancestry, affecting 1 in 2000 [1]. HS is classified as mild, moderate or severe according to the severity of the symptoms, family history and analytical presentation—hemoglobin (Hb) concentration, reticulocyte count and serum bilirubin levels [1]. When performing the classification of HS in our patients during the last years, we observed that bilirubin levels were sometimes inconsistent with the other parameters defining the severity of this anemia. This was particularly evident in some mild HS cases that presented unexpectedly high bilirubin plasma concentration, which was not in agreement with the other analytical parameters. A potential cause for this discrepancy could be the co-inheritance of HS and Gilbert’s syndrome (GS). This syndrome, which is estimated to affect 3-10% of the general population [2,3], is a metabolic disorder characterized by a mild and chronic unconjugated hyperbilirubinemia, in the absence of liver and hematologic disease. A polymorphism in the promoter of the bilirubin uridine diphosphate glucuronosyltransferase 1A1 (UGT1A1) gene, which expresses the specific isoform for bilirubin conjugation in the liver, has been shown to associate GS with a decrease of enzymatic activity to about 30% [4,5]. The majority of the GS individuals are homozygous for a TA duplication in the (TA)nAA motif of the promoter region of UGT1A1 gene [c.-41_-40dupTA]: this is characteristic of the Caucasian population [2–5], in general, as well as of the Portuguese population [6], in particular. The co-inheritance of HS and GS can exacerbate hyperbilirubinemia, and, therefore, it could be a confounding factor to define HS severity. The aim of our work was to evaluate the prevalence of GS in HS patients and how this co-inheritance may confound the clinical classification of HS and its prognosis. We evaluated bilirubin plasmatic concentration and UGT1A1 gene polymorphisms in 48 healthy individuals and in 125 patients diagnosed with HS by standard screening tests (43 splenectomised and 82 unsplenectomised). The patients were

![Fig. 1. Bilirubin plasmatic levels according to UGT1A1 polymorphism for (A) control group and total unsplenectomised HS patients (unsp HS) and (B) control group and unsplenectomised HS patients according to their clinical classification (mild, moderate or severe HS). Data presented as median values (inter-quartile range). *p < 0.05 (TA)6/(TA)7 individuals vs. (TA)6/(TA)6 individuals or (TA)6/(TA)7 individuals (Mann–Whitney U test); **p < 0.01 (TA)6/(TA)6 individuals vs. (TA)6/(TA)7 individuals (Mann–Whitney U test); ***p < 0.001 (TA)6/(TA)6 individuals vs. (TA)6/(TA)7 individuals (Mann–Whitney U test); •p < 0.05 control group vs. unsp HS patients, mild HS patients or moderate HS patients (Mann–Whitney U test); #p < 0.01 control group vs. severe HS patients (Mann–Whitney U test); $p < 0.05 control group vs. unsp HS patients, moderate HS patients or severe HS patients (Mann–Whitney U test); %p < 0.05 mild HS patients vs. severe HS patients (Mann–Whitney U test); *p < 0.01 mild HS patients vs. moderate HS patients or severe HS patients (Mann–Whitney U test).]
Table 1
Bilirubin plasmatic levels for control group and unsplenectomised and splenectomised HS patients according to clinical classification (mild, moderate or severe HS).

<table>
<thead>
<tr>
<th>Control (n = 48)</th>
<th>Bilirubin (μmol/L)</th>
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<tr>
<td></td>
<td>HS patients</td>
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<td>Total (n = 82)</td>
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<tr>
<td>Mild HS (n = 43)</td>
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<td>Moderate HS (n = 22)</td>
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<td>Severe HS (n = 14)</td>
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Data presented as median values (inter-quartile range).

**p<0.01, ***p<0.001 control group vs. HS patients (Mann–Whitney U test).
P<0.05, *p<0.01, **p<0.001 unsplenectomised vs. splenectomised HS patients (Mann–Whitney U test).

In conclusion, our data show that the co-inheritance of GS can be misleading when defining the severity of HS, and, therefore, it would be important to study the UGT1A1 gene polymorphism when the bilirubin values are not in accordance with the other parameters used to define HS severity. Moreover, it is known that the co-inherence of GS with HS increases the risk for the development of gallstones in HS children [8]; therefore, these studies could also be valuable in future clinical decisions, namely to decide about the performance of splenectomy.

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References
