Juvenile hemochromatosis associated with β-thalassemia treated by phlebotomy and recombinant human erythropoietin

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ABSTRACT

Juvenile hemochromatosis is a rare genetic disorder that causes iron overload. Clinical complications, which include liver cirrhosis, heart failure, hypogonadotrophic hypogonadism and diabetes, appear earlier and are more severe than in HFE-related hemochromatosis. This disorder, therefore, requires an aggressive therapeutic approach to achieve iron depletion. We report here the case of a young Italian female with juvenile hemochromatosis who was unable to tolerate frequent phlebotomy because of coexistent β-thalassemia trait. The patient was successfully iron-depleted by combining phlebotomy with recombinant human erythropoietin.

Key words: hemochromatosis, thalassemia, phlebotomy, rHuEPO

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Red Cells & Iron

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Examining revealed skin pigmentation, frequent premature heart beats and enlarged liver and spleen. Blood tests showed hypochromic microcytic anemia: Hb was 105 g/L, RBC 5.45×10¹²/L, MCV 64.7 fl and MCH 19.7 pg. Hemoglobin A₂ was 6%. Iron parameters and liver function tests are reported in Table 1. The biopsy showed a cirrhotic liver with heavy iron deposition both in hepatocytes and in Kupffer cells. Holter electrocardiogram recording revealed atrial and ventricular premature beats; at echocardiography ejection fraction was normal and the heart was not enlarged. Endocrine evaluation revealed hypogonadotropic hypogonadism (undetectable FSH and LH levels and lack of response to the GnRH test) and subclinical adrenal insufficiency (low basal urine-free cortisol, low levels of dehydroepiandrosterone, ACTH and absence of ACTH response to insulin-induced hypoglycemia). An oral glucose tolerance test revealed impaired carbohydrate tolerance. Free thyroid hormones and TSH were normal.

Analysis of C282Y and H63D mutations of the HFE gene gave negative results and genetic studies excluded a linkage to chromosome 6p, where the HFE gene resides. On this basis JH was diagnosed. Replacement corticosteroid and estrogen-progestogen therapy was given. A therapeutic program based on 200 mL weekly phlebotomy was planned, associated with desferrioxamine (1 g i.m. daily). However, due to concomitant β-thalassemia, the scheduled program was not completed. Phlebotomy was stopped when the patient’s Hb dropped to less than 100 g/L; in addition, the patient’s compliance with iron chelation treatment was unsatisfactory. Fourteen months later, after 30 phlebotomies (200 mL volume), the total volume of blood removed was 6,150 mL and the total iron removed (corrected for the degree of anemia) was 2,084.15 mg. To accelerate iron depletion, after informed consent, rHuEPO (150 U/kg subcutaneously twice per week) was added. During the following twenty-four months 88 phlebotomies (350 mL each) were performed. A further 10,755.55 mg of iron were removed. Overall, the total volume of blood removed was 35,850 mL and the total iron removed was 12,839.7 mg. The course of the levels of Hb serum ferritin and iron removed are illustrated in Figure 1. No adverse effects due to rHuEPO were observed. Iron parameters and liver function tests at the end of treatment are reported in Table 1. After treatment glucose intolerance improved, but hypogonadism...
continued to require specific therapy. A repeat liver biopsy confirmed liver cirrhosis but showed disappearance of iron deposition.

Discussion

Criteria for the diagnosis of JH are based on the age at presentation (before 30 years) and evidence of severe iron overload in the absence of mutations in the HFE gene. The clinical complications of iron overload include endocrine failure, especially hypogonadotropic hypogonadism and diabetes, cardiac disease, as defined by heart failure and/or left ventricular dilatation with low ejection fraction or arrhythmias requiring medical treatment and liver involvement. Genetic evidence indicates that JH is a disorder distinct from HFE 6 and mapping to chromosome 1q.8

The earlier development of severe complications in JH, as compared to hemochromatosis,9 reflects greater tissue iron deposition.10 As a consequence this disorder requires aggressive therapy which was hindered in our patient by coexistent \( \beta \)-thalassemia. We may speculate that the ineffective erythropoiesis associated with \( \beta \)-thalassemia contributes to a further increase in intestinal iron absorption, although the clinical manifestations in JH patients of comparable ages, not carriers of \( \beta \)-thalassemia, are equally severe.6,11,12

Traditional treatment by phlebotomy was unfeasible in our patient. As an alternative to iron chelation we evaluated treatment by rHuEPO associated with phlebotomy.

rHuEPO in patients with \( \beta \)-thalassemia intermedia at doses up to 500-1000 U/Kg x 3 weekly has been shown to increase total Hb in a proportion of cases.13,14 The only experience available in \( \beta \)-thalassemia trait concerns a few cases with concomitant chronic renal insufficiency. Usually these patients require a higher dosage of rHuEPO to achieve the same Hb levels as non-thalassemic controls.15

Table 1. Iron parameters and hepatic evaluation before and after treatment.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>At diagnosis</th>
<th>After treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum iron (µmol/L)</td>
<td>40.1</td>
<td>24.9</td>
</tr>
<tr>
<td>Serum transferrin saturation</td>
<td>100%</td>
<td>40%</td>
</tr>
<tr>
<td>Serum ferritin (µg/L)</td>
<td>3768</td>
<td>51</td>
</tr>
<tr>
<td>AST (U/L)</td>
<td>130</td>
<td>32</td>
</tr>
<tr>
<td>ALT (U/L)</td>
<td>94</td>
<td>26</td>
</tr>
<tr>
<td>γGT (U/L)</td>
<td>51</td>
<td>22</td>
</tr>
<tr>
<td>AlPh (U/L)</td>
<td>147</td>
<td>66</td>
</tr>
<tr>
<td>HIC (µmol/g liver dry weight)</td>
<td>55.8</td>
<td>3.13</td>
</tr>
<tr>
<td>HII (HIC/age)</td>
<td>2.7</td>
<td>0.11</td>
</tr>
<tr>
<td>Histology</td>
<td>cirrhosis</td>
<td>cirrhosis</td>
</tr>
<tr>
<td>Perls’ Prussian staining</td>
<td>4+</td>
<td>-</td>
</tr>
</tbody>
</table>

HIC = hepatic iron concentration; HII = hepatic iron index.

Increased without exacerbating the anemia. In addition, the patient’s clinical course indicated that the persistent stimulus to erythroid production provided by the rHuEPO was able to mobilize consistent amounts of iron from parenchymal tissues. To our knowledge this is the first time that this combined treatment has been used to treat severe iron overload associated with heterozygous \( \beta \)-thalassemia; this approach could be of use in other severely iron-loaded anemic patients.

Contribution and Acknowledgments

CC and UM were responsible for the design of the study and writing the paper. MDG was responsible for data collection and analysis. PP, PP and FB followed the patient clinically. All the authors gave their critical contribution to the manuscript. The name order was a joint decision considering the different contributions to the work.

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Disclosures

Conflict of interest: none.

Redundant publications: molecular characterization of this case and a partial description of the clinical phenotype is reported in Camaschella et al., Eur J Hum Genet 1997; 5:371-5. The present paper deals with the patients’ treatment. There is only overlap in the description of clinical phenotype. This is clearly stated in the paper.

Manuscript processing

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References

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