Red Cell Indices in Thalassemia Minor

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ABSTRACT

Red cell size and hemoglobin content, as measured by the Coulter Counter Model S, are consistently and rather uniformly decreased in thalassemia minor. Red cell count, hemoglobin and hematocrit are more variable and may even be normal. The finding of mean corpuscular volume (MCV) 53 to 71 $\mu^3$ and mean corpuscular hemoglobin (MCH) 17 to 25 pg should raise the suspicion of thalassemia minor. The MCV/RBC quotient is regularly under 13 in thalassemia minor and over 13 in non-thalassemic microcytosis except for some overlap in women. A presumptive diagnosis can then be made by the finding of target cells and basophilic stippling of red cells on the peripheral blood smear. Demonstration of elevated $A_2$ hemoglobin level clinches the diagnosis. (RBC = red blood cells.)

Beta thalassemia minor is an hereditary hypochromic microcytic anemia, probably a mutation favored by selection over many generations in Mediterranean peoples to provide protection against the malarial parasite.$^5,6,10$ While thalassemia minor is harmless enough, the homozygous state of the gene produces a severe anemia, thalassemia major or Cooley's anemia, which is usually fatal before adulthood.$^7$ Most patients with thalassemia minor are either not anemic or are only mildly anemic. Most are quite unaware of their condition. It is important to establish a correct diagnosis to avoid unnecessary iron treatment and to counsel patients about the possibility of thalassemia major in their offspring.

This report presents the diagnostic blood findings in a series of thalassemia minor patients. A simple stepwise procedure for making the diagnosis is outlined which can be used for inexpensive mass screening for the condition. Complete blood counts were done on 93 patients with thalassemia minor on the Coulter Counter Model S.$^*$ Peripheral blood smears were stained with Wright-Giemsa and examined in the usual manner. Quantitative hemoglobin $A_2$ levels were done by a modification of the polyacrylamide gel electrophoresis method of Bieman and Zettner.$^1$

The results of the automated blood counts are shown in table I. All of the patients with thalassemia showed significant basophilic stippling of red cells and target cells on smear, features which were not at all prominent in cases of iron deficiency anemia with red cells indices in the thalassemic range. All patients with

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$*$ Coulter Electronics, Hialeah, FL 33010.
TABLE I
PERIPHERAL BLOOD IN 93 PATIENTS WITH THALASSEMA MINOR
MEAN ± STANDARD DEVIATION

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Hemoglobin g per dl</th>
<th>Red Cell Count 10^6 per cmm</th>
<th>Hematocrit Percent</th>
<th>MCV* µL</th>
<th>MCH* pg</th>
<th>MCHC* Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men</td>
<td>29</td>
<td>12.60±1.36</td>
<td>5.98±0.48</td>
<td>37.6±3.84</td>
<td>62.8±3.88</td>
<td>20.7±1.57</td>
<td>33.13±0.86</td>
</tr>
<tr>
<td>Women</td>
<td>45</td>
<td>11.59±1.08</td>
<td>5.38±0.53</td>
<td>34.9±3.16</td>
<td>64.22±3.51</td>
<td>21.33±1.40</td>
<td>33.18±0.95</td>
</tr>
<tr>
<td>Children</td>
<td>19</td>
<td>11.29±1.15</td>
<td>5.63±0.47</td>
<td>33.84±3.26</td>
<td>59.68±3.30</td>
<td>19.7±1.10</td>
<td>33.26±1.07</td>
</tr>
<tr>
<td>Normal M</td>
<td>14-18</td>
<td>4.7 - 6.1</td>
<td>42 - 52</td>
<td>82 - 92</td>
<td>27 - 31</td>
<td>32 - 36</td>
<td></td>
</tr>
<tr>
<td>F</td>
<td>12-16</td>
<td>4.2 - 5.4</td>
<td>37 - 47</td>
<td>81 - 94</td>
<td>27 - 31</td>
<td>32 - 36</td>
<td></td>
</tr>
</tbody>
</table>

*Mean corpuscular volume  
*Mean corpuscular hemoglobin  
*Mean corpuscular hemoglobin concentration

Thalassemia minor showed elevation of hemoglobin A₂ in the 4.2 to 8.9 percent range (normal up to 4.1 percent). The t-test showed the following differences to be statistically significant: hemoglobin and hematocrit in men greater than those in women (p < 0.01); RBC in men greater than in women (p < 0.002); men's hemoglobin and hematocrit greater than children's (p < 0.002); RBC in men greater than in children (p < 0.05); MCV in men greater than in children (p < 0.01); MCH in men greater than in children (p < 0.05); MCV in women greater than in children (p < 0.01); and MCH in women greater than in children (p < 0.002). The other differences were not statistically significant.

Mean corpuscular hemoglobin concentration (MCHC), a value which is sometimes decreased in iron deficiency anemia, was normal in all but five cases. The overall thalassemic range for MCV was 53 to 71 µL and for mean corpuscular hemoglobin MCH from 17.5 to 25.4 pg.

England and Fraser recently developed a mathematical "discriminant function" (DF) to differentiate thalassemia minor from iron deficiency:

DF = MCV - RBC - (5 × Hb) - 3.4

TABLE II
DISCRIMINANT FUNCTION (DF) IN THALASSEMA TRAIT AND NON-THALASSEMA MICROCYTOSIS

<table>
<thead>
<tr>
<th></th>
<th>DF+ (Range)</th>
<th>DF− (Range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-thalassemia</td>
<td>19 (-1.3)</td>
<td>1 (-13)</td>
</tr>
<tr>
<td>*(MCV under 80)</td>
<td>2.1-60.2</td>
<td></td>
</tr>
<tr>
<td>Thalassemia trait</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>1 (2.2)</td>
<td>28 (-0.7 - -22.5)</td>
</tr>
<tr>
<td>Women</td>
<td>17 (2.6-8.6)</td>
<td>28 (0.0 - -12.8)</td>
</tr>
<tr>
<td>Children</td>
<td>2 (1.2-2.0)</td>
<td>17 (-0.1 - -24.1)</td>
</tr>
</tbody>
</table>

*Mean corpuscular volume

MCV is expressed in µL, RBC in millions per cmm and Hb in grams per dl. They found the DF regularly negative in thalassemia minor and positive in iron deficiency. In table II is shown the DF in thalassemia minor and non-thalassemic microcytosis. Mentzer proposed an even simpler formula to differentiate the two conditions: MCV/RBC; he found this quotient to be usually over 13 in iron deficiency. In table III is shown this value in thalassemia and non-thalassemic microcytosis. The MCV/RBC quotient worked for men and chil-
fren, but the thalassemic women ranged higher than 13 (up to 15.3), overlapping with the range for non-thalassemic microcytosis both in men and women. The high values for women are due partly to their significantly lower RBC and partly to their tendency toward higher MCV values. Coexisting iron deficiency was not a factor in the one thalassemic woman with MCV/RBC of 15.3; her serum iron was normal.

Screening for thalassemia minor could proceed as follows:

1. The MCV and MCH are measured, looking for values in the thalassemic range, and the MCV/RBC value is calculated.
2. Where indices and/or the MCV/RBC value are suspicious, the peripheral blood smear is examined for target cells and basophilic stippling. In a routine laboratory situation critical review of the blood film may be necessary.
3. Confirmation of the diagnosis is made by precise measurement of the A₂ hemoglobin fraction by a quantitative technique. In rare cases of thalassemia minor, A₂ hemoglobin may be normal, and hemoglobin F elevated.⁴

In studying families known to have thalassemia, A₂ hemoglobin determination on

![Figure 1. Peripheral blood smear in beta thalassemia minor showing target cells and basophilic stippling. When red cell indices are in the thalassemic range, these findings may be enough for a presumptive diagnosis of thalassemia minor. (× 1,000)](image-url)
each member is hardly necessary, the diagnosis being obvious from the cell indices and blood film. Additional laboratory tests, such as iron and iron binding capacity, osmotic fragility, bone marrow examination and the usual hemoglobin electrophoresis done for hemoglobinopathy, are superfluous in most cases. Alpha thalassemia trait is also prevalent in Mediterranean and Oriental peoples\textsuperscript{8,10} and may be present when the MCV/RBC value and the peripheral blood smear suggest thalassemia although hemoglobins A\textsubscript{2} and F are normal.\textsuperscript{9} Erythrocyte morphology may be normal in alpha thalassemia trait, however.\textsuperscript{10}

References