Spotlight on hematology

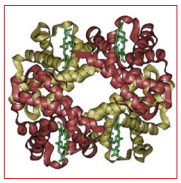
Hematological Findings with Beta Thalassemias

MQZH 2012-01

Introduction

Thalassemia are genetically caused anomalies of the quantitative globin chain synthesis of hemoglobin. Depending on the affected chain, they are grouped into alpha- and beta- thalassemia. Beta-thalassemias are especially widespread in the Mediterranean area. Depending on the genetic defect and clinical characteristics, a distinction is made between thalassemia minima, minor, intermedia and major. The associated disease pictures range from completely asymptomatic carriers with thalassemia minima/minor who do not require treatment to thalassemia major where already during infancy transfusion requiring anemia and skeletal anomalies appear. In the presence of microcytoses, iron deficiency and thalassemias rank first in the differential diagnosis.
A suspicion can already usually be raised based on the quantitative blood count. Our proficiency testing survey sample 2012-01 is from a 50-year-old patient with beta thalassemia intermedia (after splenectomy).

Pathogenesis



Human hemoglobin consists of two components: the iron-containing and oxygen-binding hem group and the globins (proteins), which are composed of different combinations of chains (α, ß, γ, δ). In beta thalassemia, a genetic defect causes few or no ß-chains at all to be produced. The α-chains, which are relatively increased as a result, are unstable and clump together (precipitates). These precipitates lead to early deterioration of erythroblasts in the bone marrow or to accelerated degradation of mature erythrocytes in the periphery (ineffective hematopoiesis, hemolysis).
The body makes an attempt to compensate for this reduction with erythropoietin by increased stimulation of erythropoiesis. In thalassemia intermedia and major, the massive hyperstimulation leads to a 20-30-fold expansion of the blood-forming bone marrow (risk: skeletal deformities) and increased resorption of iron from food (danger: iron deposits in liver, heart, pancreas). Further complications arise from the disease itself but also from therapeutic interventions.

Quantitative hematological findings in comparison

Parameter	*Iron Deficiency*	*ß thalassemia minor*	*ß thalassemia intermedia*	*ß thalassemia major*
Erythrocytes	normal to↓	↑ to normal	↓	↓
Hemoglobin	↓	normal bis ↓	↓ *thalassemia intermedia endogenous production > 80 g/L, occasional transfusion requirement*	↓ *thalassemia intermedia endogenous production < 80 g/L, occasional transfusion requirement*
MCV[1)]	↓	↓ (< 78 fl)	↓	↓
MCH[1)]	↓	↓ (< 27 pg)	↓	↓
RDW	↑	normal to ↑	↑	↑
Blood picture general	- Hypochromia - microcytosis - aniso-poikilocytosis	- microcytosis - Hypochromia	*like Th.minor +* - pronounced anisocytosis - poikilocytosis	*like Th.minor +* - pronounced anisocytosis - poikilocytosis
Blood picture typical characteristics	- ovalocytes	- basophilic stippling often coarse	- basophilic stippling often coarse	- basophilic stippling often coarse
Blood picture facultative changes	- target cells - anulocytes in dependence of MCH	- target cells not evidencing - anisocytosis	- spherocytes - teardrop forms - Pappenheim bodies - polychromesia *post splenectomy:* - acanthocytes - Howell-Jolly bodies	- spherocytes - teardrop forms - Pappenheim bodies - polychromesia *post splenectomy:* - acanthocytes - Howell-Jolly bodies
Erythroblasts[2)]	none	none	often	always

1) normochromic-normocytic Erc indices are rarely possible: e.g. rare genetic constellations („silent“ thalassemia), simultaneous folic acid deficiency, pronounced polychromasia (reticulocytosis), status post blood transfusions.
2) In the blood picture > 4 erythroblasts per 100 leukocytes: manual correction of the instrument leukocyte value required!

Thalassemia versus iron deficiency

With the hypochromic-microcytic blood picture, iron deficiency and thalassemia minor must be distinguished from each other in a first step. The calculation of the „Meltzer Index“ may be helpful here. However, it can only be calculated or interpreted when microcytosis is present (decreased MCV):

Mentzer Index (MI)

$$\frac{MCV\ (fl)}{Ec\ (T/l)} = MI$$

MI > 13 more likely iron deficiency
MI < 13 more likely beta-thalassemia

If iron deficiency is detected in the laboratory, thalassemia can be ruled out only after the iron deficiency was corrected for.

Thalassemia and desire for children

It is important that people with thalassemia are informed about the possibility of inheritance and the associated risks. For example, the children of a mother and a father with thalassemia minor have a 25% risk of falling ill with thalassemia major.
When couples have a desire to have children, prior genetic diagnosis and consultation is therefore important.

Spotlight on hematology

Correction of the leukocyte count with washing out of erythroblasts

Since erythroblasts are nuclei-containing cells, they are counted as leukocytes by hematology instruments. With a proportion of > 4 erythroblasts per 100 leukocytes (WBC), the WBC count must therefore be corrected manually:

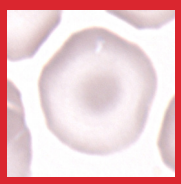
$$\frac{100 \times \text{WBC no. device}}{100 + \text{no. Ebl. per 100 WBC}} = \text{WBC corr.}$$

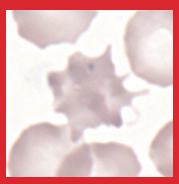
Here is the calculation example for our thalassemia patient

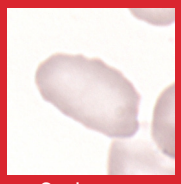
WBC device 15.65 G/l
Erythroblasts per 100 WBC 138

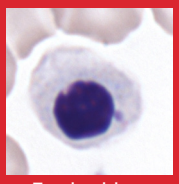
$$\frac{100 \times 15.65}{100 + 138} = 6.58\ g/l\ \text{leukocytes}$$

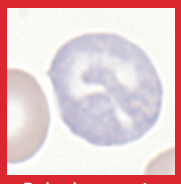
Pictures from proficiency testing survey 2012-01

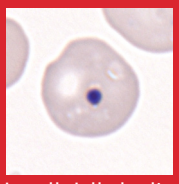

Target cells

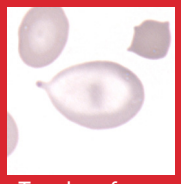

Acanthocytes

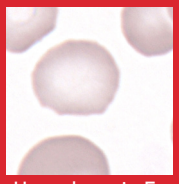

Ovalocytes


Erythroblast


Polychromasia


Howell-Jolly bodies


Teardrop forms


Hypochromic Ec

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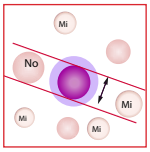
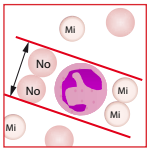
Morphological findings of thalassemia in the blood picture

Microcytosis (MCV)

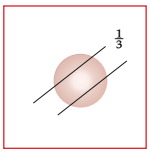
Microcytosis is the main finding in thalassemia minor.

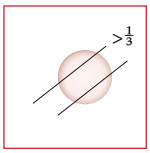




Hypochromasia (MCH)

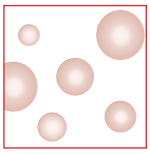
The pronounced hypochromasia of the erythrocytes can also be seen well in microscopy. The central brightening of the erythrocytes is seen in significantly more than 1/3 of the erythrocyte. Target cells are also evaluated as hypochromic.





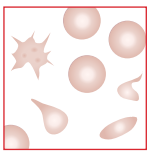
Anisocytosis (RDW)

Anisocytosis is understood as an increase in the size variability of a patient's erythrocytes. Morphologically, normo-, micro- and macrocytes are detected simultaneously.



Poikilocytosis

Poikilocytosis is understood as the simultaneous occurrence of different, non-round forms in a blood smear.



Special forms of erythrocytes and erythrocyte inclusions

1. Target cells

Erythrocytes with hemoglobin ring and central hemoglobin dot.

2. Acanthocytes

Almost round cells with 2 to 20 irregularly distributed spines of different lengths on the surface.

3. Spherocytes

Small, spherical and dark-red appearing erythrocytes with no central brightening.

4. Teardrop forms

Teardrop-shaped erythrocytes. The tapering part of this cell is round or truncated at its end.

5. Ovalocytes (elliptocytes)

Elongated, oval to rod-shaped erythrocytes.

6. Basophilic stippling (fine, coarse)

Basophils stippling (dotting) can be fine and regular or coarse and irregular. In beta-thalassemias, they correspond to precipitates of the unstable alpha chains.

7. Pappenheim bodies

Are (bright-) basophils iron-containing inclusions in erythrocytes. They are often found in pairs (doublets) or in aggregates (clusters) at the cell periphery. The iron content of these inclusion bodies can be confirmed by Berlin blue stain.

8. Howell-Jolly bodies

Dark basophilic, round erythrocyte inclusions located individually mostly at the cell periphery. They are remaining nuclear cell fragments of erythroblasts. They are typically found after splenectomy.

9. Polychromatic erythrocytes (polychromasia)

Reddish-blue (lighzyt purple) stained erythrocytes. They correspond to still immature erythrocytes, which have recently left the bone marrow (correspond mainly to reticulocytes).