

Case Report

Corpuscular Haemolytic Anaemias - Lepore Haemoglobinopathy

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ABSTRACT: Haemoglobinopathies are hereditary conditions in which the fundamental lesion affects the synthesis rate or the structure of the globin in normal hemoglobin. The synthesis of the polypeptide chains in globin is genetically coded. Clinically, haemoglobinopathies manifest most commonly in the form of hemolytic anemia and, more rarely, cyanosis and polyglobulia. They differ from “acquired haemoglobinopathies”, such as methemoglobinemia, in which hemoglobin is usually compromised due to the action of toxic substances. The clinical aspects are in close relationship to the nature and level of the structural anomaly of the Hb molecule. The heterozygous form of the Lepore syndrome is hematologically characterized by a similar pattern to minor β -thalassemia and electrophoretically by abnormal Hb D fractions at a rate of 5-10% and a decreased percentage of HbA. In homozygous forms, Lepore Hb represents 10-20% on electrophoresis, the rest consisting of HbF; HbA and HbA2 are completely absent. From a clinical point of view, Hb Lepore heterozygotes are similar to those with minor β -thalassemia.

KEYWORDS: haemoglobinopathie, hemoglobin D

Introduction

Haemoglobinopathies are hereditary conditions in which the fundamental lesion affects the synthesis rate or the structure of the globin in normal hemoglobin. The synthesis of the polypeptide chains in globin is genetically coded. The genetic message comprised in the nucleotide sequence of chromosomal DNA is transmitted through the ribosomesmRNA and then translated into the amino acid sequence of the polypeptide chain. Each chain contained by physiological hemoglobin is represented in the chromosomal DNA by a particular gene, named after the specific chain: ξ , ϵ , α , γ , δ , β .

Hemoglobin genes are located on two pairs of autosomal chromosomes: pair 16 contains genes ξ and α , while pair 11 contains non-alpha genes: ϵ , $G\gamma$, $A\gamma$, δ and β . The more than 500 abnormal Hb that have been discovered so far are caused by lesions of hemoglobin structural genes. These genetic irregularities alter the normal nucleotide sequence of the gene and thus the genetic message, which reflects on the structure of the corresponding polypeptide chain. The replacement of a single aminoacid in globin polypeptide chains, which is caused by a point mutation, leads to the synthesis of abnormal hemoglobins.

Material and Method

We present the case of patient D.L. from the records of Filantropia Municipal Hospital, who was admitted to the Ob-Gyn Department with the diagnosis “IIGIP 38 weeks pregnancy, single living fetus, eutocic pelvis, uterine scarring, labor; anemic syndrome”. For impending uterine rupture and uterine scarring she gives birth by OCST to a male enfant, 3300 g., Apgar 9, 50 cm in length. The postoperative evolution was favorable under administration of antibiotic treatment (ampicillin1g/6h, gentamicin 80 mg/12h), anti-inflammatory drugs (Ketonal 1f/24h), anticoagulants (Fraxiparine 0.4ml/24h), uterotonic medication (oxytocin 5ui/12h, calcium gluconate1f/24h) and folic acid 10mg/24h.

Results

The paraclinical investigations performed on both mother and newborn revealed:

Table 1. Mother Complete Blood Count

Parameter - mother	Result	Biological reference values
Leukocytes	14.14	$4-9 \times 10^3/\text{mm}^3$
Erythrocytes	4.07	$4.0-5.0 \times 10^6/\text{mm}^3$
Hemoglobin	9.0	12-15 g/dl
Hematocrit	27.1	36-45%
MCV	66.6	88-95 fL
MCH	22.1	28-32 pg

MCHC	33.2	32-36 g/dl
Platelets	231	150-400
Lymph%	7.6	20-40%
Mono%	7.1	0-8%
Neut%	85.0	50-75%
Eos%	0.2	0-3%
Baso%	0.1	0-1%
Lymph#	1.07	1.9-11.5 x 10 ³ /mm ³
Mono#	1.01	0.1-1.7 x 10 ³ /mm ³
Neut#	12.2	1.2-7 x 10 ³ /mm ³
Eos#	0.03	0.1-0.8 x 10 ³ /mm ³
Baso#	0.01	0-0.2 x 10 ³ /mm ³
RDW-CV%	17.2	11-17.5%
RDW-SD	39.7	37-54 fl
PDW	18.1	11-15 fl
MPV	11.4	7.4-10.2 fl
P-LCR%	37.2	13-43%
PCT	0.26	0.2-0.3%

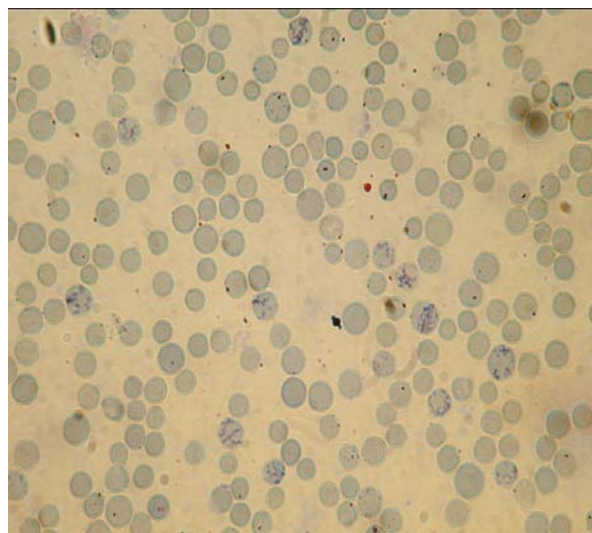


Fig.2. Blood smear: reticulocytes

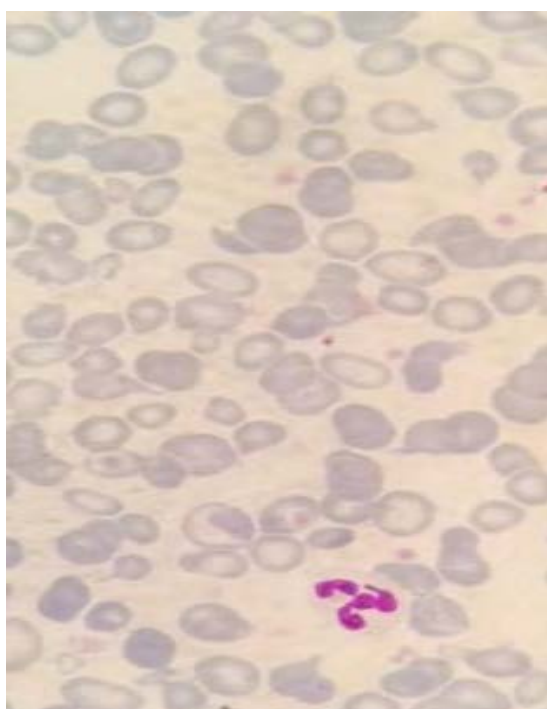


Fig.1. Blood smear: col. MGG; Leukocyte formula:
1% metamyelocytes, 2% non-segmented neutrophils, 76% segmented neutrophils, 13% lymphocytes, 7% monocytes, eosinophils 1%. Blood smear showed hypochromic microcytes and moderate poikilocytosis, with "target", "tear-drop" RBC and schizocytes.

Table 2. Mother Biological Parameters

Parameter - mother	Result	Biological reference values
Sideremia	47	49-165 µg/dl
Ferritin	6.4	5-124 mg/ml
Reticulocytes	9%	0.5-2%

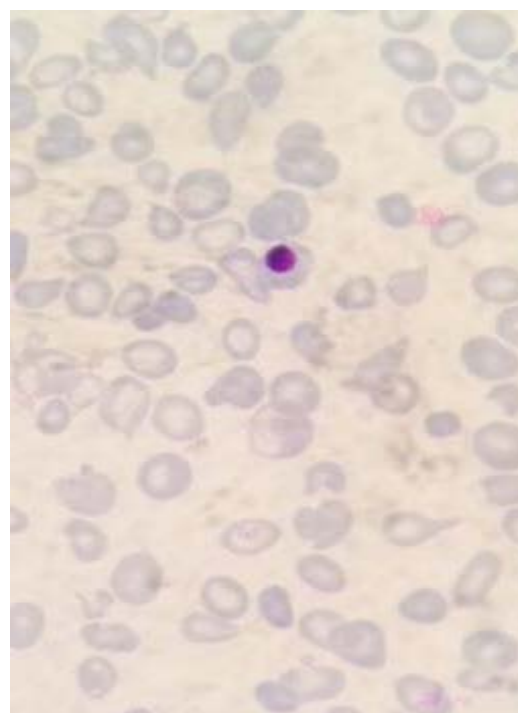


Fig.3. Blood smear: col. MGG; Blood smear showed 1% oxyphilic erythroblasts and moderate poikilocytosis, "target" and "tear-drop" erythrocytes and rare schizocytes.

Table 3. Hemoglobin Electrophoresis - Mother

Hemoglobin Electrophoresis - mother	Result	Biological reference values
Hb A	85.5%	96.7-97.8%
Hb A2	2.5%	2.2-3.2%
Hb F	3.3%	0.0-0.5%
Comments	Hb D - 8.7%	0%

Table 4. Newborn Complete Blood Count

Parameter– newborn	Result	Biological reference values
Leukocytes	18.02	4-12 x 10 ³ /mm ³
Erythrocytes	4.9	4.5-6.0x10 ⁶ /mm ³
Hemoglobin	17.4	15-19 g/dl
Hematocrit	46.5	39-54%
MCV	94.9	88-95 fL
MCH	35.5	30-37 pg
MCHC	36.0	32-36 g/dl
Platelets	312	150-400
Lymph%	36.2	35-65%
Mono%	9.4	0-15%
Neut%	52.9	20-40%
Eos%	1.1	0-3%
Baso%	0.4	0-1%
Lymph#	6.53	1.9-11.5x10 ³ /mm ³
Mono#	1.69	0.1-1.7 x 10 ³ /mm ³
Neut#	9.52	1.2-7 x 10 ³ /mm ³
Eos#	0.2	0.1-0.8 x 10 ³ /mm ³
Baso#	0.08	0-0.2 x 10 ³ /mm ³
RDW-CV%	17.1	11-17.5%
RDW-SD	56.7	37-54 fl
PDW	12.3	11-15 fl
MPV	10.1	7.4-10.2 fl
P-LCR%	26.2	13-43%
PCT	0.32	0.2-0.3%

Table 5. Newborn Biological Parameters

Parameter– newborn	Result	Biological reference values
Sideremia	117	30-162 µg/dl
Ferritin	396.4	28-365 mg/ml
Reticulocytes	10%	0.5-2%

Table 6. Hemoglobin Electrophoresis - newborn

Hemoglobin Electrophoresis - newborn	Result	Biological reference values
Hb A	21.7%	>1year: 96.7-97.8%
Hb A2	0.8%	>1 year: 2.2-3.2%
Hb F	77.5%	>1 year: 0.0-0.5%

Discussion

The reduced erythrocyte lifespan is the major criterion which defines pathological hemolysis and differentiates it from the normal, physiological one. The response of the organism to this loss consists of a compensatory increase of erythrocyte production in the bone marrow – *hyper-reticulocytosis*.

If the erythrocyte destruction through hemolysis is completely compensated by the bone marrow, the number of circulating red blood cells remains within normal limits. This

situation is called “hemolysis state” or “compensated hemolysis”.

Unlike *physiological hemolysis*, which concerns a lower number of red blood cells consisting of only those that have reached their maximum lifespan, *pathological hemolysis* affects all circulating erythrocytes, thus causing the early destruction of an abnormally high cell quantity per time unit.

Hemolysis is the process of removing erythrocytes from circulation. In physiological conditions, hemolysis is the mechanism by which aged erythrocytes are removed from circulation. Towards the end of their existence, erythrocytes acquire some adverse physical and immunological attributes:

- they become more rigid - this hinders the passing of senescent erythrocytes through the splenic cords, thus being subjected to unendurable metabolic stress;

- they express a senescence antigen embedded in a membrane protein - "Band 3"; this antigenicity triggers an autoimmune response: IgG autoantibodies cover erythrocytes and mediate their adhesion to Fcγ receptors expressed by spleen macrophages. The adhesion of the erythrocytes to the macrophages is followed by their ingestion and digestion. The spleen is credited as the most important organ of selection and elimination of senescent erythrocytes. This phenomenon is called *extravascular or intratissular hemolysis* and it represents the mechanism by which approximately 90% of senescent red blood cells are eliminated.

In physiological conditions, about 5-10% of erythrocytes are also lysed inside the blood stream - *intravascular hemolysis*, a process by which hemoglobin is released in plasma and then processed in the liver and kidneys. These natural losses are continuously replaced by an equal production of reticulocytes from the bone marrow. Thus, the entire amount of red blood cells is renewed in about three months, also maintaining a normal number of circulating cells.

Clinically, haemoglobinopathies manifest most commonly in the form of hemolytic anemia and, more rarely, cyanosis and polyglobulia. They differ from “acquired haemoglobinopathies”, such as methemoglobinemia, in which hemoglobin is usually compromised due to the action of toxic substances.

The clinical aspects are in close relationship to the nature and level of the structural anomaly of the Hb molecule.

Haemoglobinopathies can be divided into two groups:

**qualitative haemoglobinopathies* - include those in which the anomaly or mutation leads to the synthesis of chemically abnormal hemoglobin

**quantitative haemoglobinopathies* - include thalassemia syndromes characterized by partial or complete blockage of the synthesis rate of one or more globin polypeptide chains.

The haemoglobinopathy diagnosis is suggested by:

- medical history –a condition that has been evolving since childhood;
the same signs are also present in other family members
- physical signs: jaundice or sub-jaundice, splenomegaly, cyanosis
- common laboratory exams that highlight anemia, signs of hemolysis and morphological changes of the erythrocytes.
- special examinations, which reveal the abnormal hemoglobin - Hb electrophoresis;

Evolution and prognosis:

Hb D heterozygous forms usually have a good prognosis and are compatible with an almost normal life, except for some cases that can progress to severe haemolytic anemia.

Treatment

- symptomatic treatment of the disorders caused by genetic damage and by the various complications that occur during chronic disease progression; periodic administration of folic acid and group B vitamins.
- bone marrow transplantation, especially in the homozygous form
- genetic counseling - prevention in order to limit the spread of the genetic anomaly specific to these diseases.

Conclusions

1. The heterozygous form of the Lepore syndrome is hematologically characterized by a

similar pattern to minor β -thalassemia and electrophoretically by abnormal Hb D fractions at a rate of 5-10% and a decreased percentage of HbA. In homozygous forms, Lepore Hb represents 10-20% on electrophoresis, the rest consisting of HbF; HbA and HbA₂ are completely absent.

2. From a clinical point of view, Hb Lepore heterozygotes are similar to those with minor β -thalassemia.

3. It was not possible to prove the transmission of this genetic condition to the newborn, as hemoglobin electrophoresis is inconclusive during the first year of life.

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