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Case report

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Vesna Bogicevic, Gordana Kostic
Danijela Jovancic
Gordana Bjelakovic, Mira Ilic
Bojko Bjelakovic, Ljiljana Pejcic
Verica Ilic

Children's Internal Clinic
Clinical Centre Nis

CASE REPORT OF A PATIENT WITH THALASSEMIA AND HEMOGLOBIN LEPORE

SUMMARY

Thalassemias are inherited disorders of hemoglobin synthesis, characterized by reduced output of one or other globin chains of adult hemoglobin. The red blood cells are vulnerable to mechanical injury and die easily. To survive, many people with thalassemia need blood transfusions at regular intervals. Hereby, we present the case of a six-year-old boy, I.U. from Zitoradja, who was admitted to the Children's Internal Clinic in Nis in July 2005, due to paleness, exhaustion, higher body temperature, vomiting and diarrhoea. During hospitalization, autoimmune haemolytic anemia was dismissed and therapy was administered against infection with supplementation of folic acid and vitamin B12. Although no members of the nuclear family had similar symptoms, based on the findings of the boy's abdominal ultrasound examination, as well as enlarged spleen and data on the previous non-responsive treatment of anemia with iron medicine, there arose a doubt that it was the case of hereditary haemolytic anemia. Molecular genetic examination of the boy revealed heterozygosity for beta thalassemia and Hb Lepore, a rare type of hereditary haemolytic anemia at the territory of Serbia. During the last two years from the diagnosis, the boy has been in good condition and has not fallen behind in growth and development in relation to his mates. The values of haemoglobin have been maintained at satisfactory level, and so far, no erythrocyte transfusion has been applied. Splenectomy is planned to eliminate subjective discomfort that the boy has been feeling last months.

Key words: **ß-thalassemia, hemoglobin Lepore, splenomegaly**

INTRODUCTION

Thalassemias are a group of genetic disorders of hemoglobin (Hb) synthesis, characterized by decrease in creation of one or more globin chains (1). In 1925, Thomas Cooley and Pearl Lee described a form of severe anemia occurring in children of Italian origin, associated with splenomegaly and characteristic bone changes. Because all early cases were reported in children of Mediterranean origin, the disease was later termed thalassemia, from the Greek word for sea, *thalassa* (2). It has been estimated that there are 180 million people who are heterozygotic carriers of various types of thalassemia throughout Asia, North Africa, and Europe. This high frequency of genes results in a significant annual number of births of homozygotic gene carriers and complex heterozygotic conditions (double heterozygot) that remain clinical problems (3,4).

Thalassemias are classified, according to the particular globin chain that is ineffectively produced, as ά, β, δβ and γδβ thalassemias. Thalassemia, which

Corresponding author. Tel/fax 018/514-014 064/1810-880

is caused by a decrease in the production of β-globin chains, affects multiple organs and is associated with considerable morbidity and mortality (5). The symptoms start when the γ chain production is switched off and the β chains fail to form in adequate numbers (1). Manifestations of anemia include extreme pallor and enlarged abdomen due to hepatosplenomegaly (4).

In many populations in which thalassemia is common, the genes for structural hemoglobin variants such as hemoglobins S, C, and E are also common, so it is not unusual for individuals to inherit a gene for thalassemia from one parent and that for a hemoglobin variant from the other. A combination of Hb Lepore with β-thalassemia results in a severe clinical condition resembling β-thalassemia major. Most of the important forms of thalassemia are inherited in a Mendelian recessive fashion (6). When one parent carries the β-thalassemia trait and the other parent the Hb Lepore trait, there is a 25% chance in each pregnancy that the child will be born with HbLepore/β-thalassemia.

Treatment of patients with β-thalassemia major has improved dramatically during the past 40 years; however, the current clinical status of these patients remains poorly characterized (7). Regular red blood cell transfusions eliminate the complications of anemia and compensatory bone marrow expansion, permit normal development throughout childhood, and extend survival. In parallel, transfusions result in a "second disease" while treating the first, that of the inexorable accumulation of tissue iron that, without treatment (use of chelating therapy), is fatal in the second decade of life (5,8).

CASE REPORT

The boy I.U. six years of age, from Zitoradja, was admitted to the Children's Internal Clinic in Nis in July, 2005, due to paleness, exhaustion, and higher body temperature.

Anamnesis*:* One day prior to admission, the boy got high body temperature (39,4°C) followed by headache, stomach pain, diarrhoea, and vomiting. Parents reported that in the last few months he had been paler than usual, which was the reason why the outpatient department doctor sent them for a hospital examination and treatment.

From personal anamnesis we learn that it was the second child from the fourth pregnancy (the two prior terminated willingly). The delivery was in term, the baby was born vital, 4400/56. Early psychomotor development was proper. Since the boy was two years of age, sometimes, his urine has been dark-coloured and had severe paleness which lasted for a few days. Except for often colds, up to now he has been treated in the outpatient department with iron medicines because of anemia, yet without significant improvement in the blood quality.

In the family anamnesis there was no evidence of similar symptoms in the members of the nuclear family.

From the status*:* On admission, the boy aged 6 years, conscious, subfebrile, eutrophic, BM 23kg, eupnoic RF 24/min, tachycardia SF 132/min, distinctly pale-yellow skin colour and visible mucus tissue, preserved muscle tonus, turgor, and skin elasticity.

From the systems' findings we registered the presence of light hyperaemia of palatal arches, systolic noise over the entire precordium, painful sensitivity of abdomen to palpation and spleen enlargement for three transversal fingers bellow the left rib arch. The other systems findings were clear.

Laboratory and clinical examination*:*
Blood test results showed low values of erythrocytes (3,2x1012), haemoglobin (6,8g/dl), and hematocrit (22%), while the values of leukocytes and thrombocytes were within the range of referential values. The number of reticulocytes was 8/1000. On the preparation - distinctive anisopoikilocytosis – erythrocytes in the tear shape, fragmentary elyptocytes and a sporadic acidophilic erythroblasts.

Urine: dark yellow to red colour, albumin in traces, urobilinogen positive, haemoglobin negative. In urine sediment - sporadic leukocytes, plenty of amorphous salts.

Biochemical examinations: glycaemia, urea, creatinine, hepatogram, overall proteins and acidobasic status within the range of referential values. Total bilirubin 37,35 μmol/l (ref.values:0-20,52), indirect bilirubine 37,35 μmol/l (ref. values:5,13-15,39), direct bilirubin negative. Serum iron 14.2 μmol/l(ref.values:12,5-23,2), TIBC 42,2mol/l (ref.values:45-63), UIBC 28 μmol/l(ref.values:34,5-40,2). The LDH values increased (697), and ferritin normal.

Direct Coombs test negative.

Sodium in erythrocytes 14.8 μmol/l (ref.values:18-21), Potassium in erythrocytes 91.6 μmol/l (ref. values: 80-86). Osmotic resistance of erythrocytes positive.

Electrophoresis of hemoglobin – HbA1 32,7%, HbS 64,3%(0%), HbA2 3% . Normal adult hemoglobin contains the following components: HbA(95-98%), HbA2(2-3%), HbA1(3-6%) and HbF(<1%).

Myelogram – hypercellularity of bone marrow. There are all developmental forms of all three myeloid threads, without morphological changes. Distinctively irritated erythroid thread.

Abdomen ultrasound examination: liver, gallbladder, pancreas, and kidneys of normal echo-finding. Spleen diameter over 15cm, homogenous, with free hilus. Paraaortal and paracaval spaces free.

RTG pulmo et cor: Radiological finding of lungs and heart normal.

During hospitalization, in order to deal with infection and correct the anemia, the parenteral antibiotic and corticosteroid therapy, Folic acid replacement and Vit. B12 with intravenous rehidration were administered. After ten days, the boy was discharged in good condition. The advice was to continue with Folan therapy and decrease cortico therapy according to the scheme until cessation. Because of the doubt of hereditary hemolitic anemia and impossibility of molecular-genetic examination in our institution, the boy and his parents were directed to the Research Center for Genetic Engineering and Biotechnology in Skoplje, to professor dr G.D.Efremov.

The following findings of hemoglobin analysis were obtained *(Figure 1)*.

МАКЕДОНСКА АКАДЕМИЈА НА НАУКИТЕ И УМЕТНОСТИТЕ
Истражувачки центар за генетско инженерство и биотехнологија
Бул. Крсте Мисирков 2, 1000 Скопје, Република Македонија

Проф. Др. Георги Д. Ефремов
Професор и Директор

Тел: (389 02) 32 35 410
Факс: (389 02)3115 434
E-mail: gde@manu.edu.mk

ХЕМОГЛОБИНОЛОШКИ АНАЛИЗИ

ИМЕ И ПРЕЗИМЕ НА ПАЦИЕНТОТ : И[illegible] У

УПАТЕН ОД: Др.Весна Богичевиќ, Хематологија-Мед. Факултет, Ниш

ДАТУМ НА ПРИМАЊЕ НА КРВ: 11.08.05 **R. бр. 4231+M+T**

РЕЗУЛТАТИ:	Пропозитус	Мајка	Татко
Hb g/dl:	8.5	10.8	14.0
Er x 10^{12}l:	4.19	5.4	6.41
He vol%:	28.0	35.0	44.9
MCV fl:	67.0	65.7	70.0
MCH pg:	20.4	20.0	21.8
Електрофореза на S.G.:	HbAF±80%+Lepore+HbA$_2$	HbA+Lepore(±10%)+A$_2$	HbA+Hb
Hb-Fad % (норм.<1%):	80.0	1.2	1.3
Hb A2 % (норм. до 3.5%):	10.0	10.5	4.4
HPLC: HbF (%)	51.0		
HbA$_0$ (%)	27.0	81.0	92.3
Lepore(%)	9.0	11.1	
HbA$_2$ (%)	2.4	3.0	4.2
HbAF+A1c(%)	9.0	4.5	3.3
HPLC (C4): Hb Lepore (%):	4.2		
AγT (%):	12.7		
Gγ (%):	46.6		
AγI (%) :	40.7		
Осмот. Резист. на Er:	(+) (+)	(+) (+)	(+) (+)
Инклузиони телца:			
Топлотен тест за стабилност:	(-)	(-)	(-)
PCMB тест:			
Methemoglobin % (норм. 3%):			
n-butanol test:	(-)	(-)	(-)
In vitro биосинтеза на Hb ^{3}H-Leu (α/γ+β)	1.46		
Тип на мутација	HbLepore/IVS-I-6	A/HbLepore	A/IVS-I-

Наод: Пацијент У[illegible] И[illegible] је двојни хетерозигот за β таласемија и Hb Lepore. Молекуларна карактеризација β глобинских гена је показала да је ген наслеѓен од мајке хибридни ген чијом контролом се ствара Hb Lepore, док ген наслеѓен од оца је мутиран у 6-ом нуклеот прве интервентне секвенце (IVS-I-6). Мајка пацијента је носилац (хетерозигот) за Hb Lep док је отац носилац (хетерозигот) за β таласемија (IVS-I-6).

ПРОВЕРИЛ:
Акад. Георги Д. Ефремов

Скопје 22.08.2005

Figure 1. Familial haemoglobin analysis

DISCUSSION

The patient I.U. is a double heterozygote for β-thalassemia and Hb Lepore. Molecular characterization of beta globin genes showed that the gene inherited from the mother was a hybrid gene under whose control Hb Lepore was created, while the gene inherited from the father was mutated in 6th nucleotide of the first interventive sequence (IVS-I-6). The mother of the patient is the carrier (heterozygote) for HbLepore, while the father is the carrier (heterozygote) for beta-thalassemia (IVS-I-6).

After diagnosis**,** during the previous two years, the boy was under constant hematological control, that included regular blood control, occasional checks of ferritin level, and ultrasound examination of the spleen diameter. He was in a good condition, and did not fall behind in growth and development in relation to his mates. Fifteen days a month, he took tabletes Folan. The aim was early prevention and curing of infections. Until a few months ago, hemoglobin values were in the range of 8,3 to 10 g/dl, so that there has not been any erythrocyte substitution so far. However, at the last check-up, the hemoglobin values were up to 8,5g/l., the spleen diameter at the last control was 17cm (normal diameter for that age being 8,5 – 11cm), and the boy complained of occasional discomfort in the sense of swelling and weight in the stomach. As splenomegaly is obviously aggravating the anemia and disturbs the boy's acitivity by pressing the abdomen organs, splenectomy is planned after vaccination.

CONCLUSION

We presented a patient with intermediary type of beta-thalassemia which is rare in our country, but frequently occurs in the population of the neighbouring countries - Macedonia, Greece, South Italy. Due to constant migrations during last ten years, we may expect higher occurence of these hereditary types of hemolytic anemias. Diagnostic procedures should be directed towards discovering molecular-genetic abnormalities of hemoglobin, unless there are no usual reasons for its occurrence in the patient with anemia.

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PRIKAZ PACIJENTA SA ß - TALASEMIJOM I HEMOGLOBINOM LEPORE

Vesna Bogićević, Gordana Kostić, Danijela Jovančić, Gordana Bjelaković, Mira Ilić, Bojko Bjelaković, Ljiljana Pejčić, Verica Ilić

Dečija interna klinika Kliničkog centra Niš

SAŽETAK

Talasemije su nasledne bolesti sinteze hemoglobina koje se karakterišu smanjenom proizvodnjom jednog ili drugog globinskog lanca adultnog hemoglobina. Eritrociti su podložni mehaničkim ostećenjima i lako stradaju. Transfuzije krvi u odredjenim vremenskim periodima su nekim ljudima koji boluju od talasemije potrebne za preživljavanje. Prikazujemo šestogodišnjeg dečaka I.U. iz Žitoradje, koji je jula 2005. godine primljen na Dečiju internu kliniku u Nišu zbog bledila, malaksalosti, povišene telesne temperature i simptoma gastroenterokolitisa. Tokom hospitalizacije isključena je autoimuna hemolizna anemija i primenjena terapija u cilju sanacije infekcije uz suplementaciju Folnom kiselinom i Vitaminom B12. Iako niko od članova uže porodice nije imao slične tegobe, kod dečaka je na osnovu ultrazvučnog nalaza uvećane slezine i podataka o prethodno bezuspešnom lečenju anemije preparatima gvoždja, postavljena sumnja da se radi o naslednoj hemoliznoj anemiji. Molekularno genetskim ispitivanjem, kod dečaka je otkrivena heterozigotnost za beta talasemiju i Hb Lepore, redak oblik nasledne hemolizne anemije na prostorima Srbije. Tokom protekle dve godine od dijagnoze, dečak je u dobroj kondiciji i ne zaostaje u rastu i razvoju u odnosu na vršnjake. Vrednosti hemoglobina se održavaju na zadovoljvajućem nivou, te do sada ni jednom nije primenjena transfuzija eritrocita. Planira se splenektomija radi otklanjanja subjektivnih tegoba koje dečak oseća poslednjih meseci.

Ključne reči: **talasemija, hemoglobin Lepore, splenomegalija**