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SHORT COMMUNICATION

Hb H Disease Diagnosed During Adolescent Pregnancy

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ABSTRACT

Hb H disease is a moderate to severe form of α-thalassemia (α-thal). Patients with Hb H disease may become symptomatic, especially during infections and pregnancy, and may require transfusions. Herein, we present a 16-year-old female with Hb H disease who was initially diagnosed during adolescent pregnancy and was found to carry the $-\alpha^{3.7}/-(\alpha)^{20.5}$ deletions. The relatively mild presentation of this case highlights the milder phenotypic consequences of deletional α mutations. The case describes the screening and management of pregnancy with Hb H disease. Additionally, this case demonstrates that screening of some undiagnosed inherited blood disorders is important during pregnancy.

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Adolescent pregnancy; deletional α mutation; Hb H disease

Hb H disease is a mild-to-severe form of inherited autosomal recessive α-thalassemia (α-thal), and is more common in Mediterranean countries, the Middle East, and South East Asia [1]. Hb H disease usually occurs as a result of deletions of three α globin genes; however, nondeletional mutations such as Hb H/Hb Constant Spring (*HBA2*: c.427T>C) may also occur. The patients have mild-to-severe anemia, hypochromia, microcytosis, and an average or slightly reduced level of Hb A_2, along with a variable quantity of Hb H (0.8–40.0%) [1]. Excess β-globin chains in the presence of decreased α-globin production form β4 tetramers, namely Hb H, which may be detected by globin electrophoresis and by staining of blood smears with brilliant cresyl blue [2]. The patients may become symptomatic, especially during infections, and may require transfusion therapy. Herein, we present a patient with Hb H disease, initially diagnosed during an adolescent pregnancy.

Case report

A 16-year-old female presented at the obstetrics and gynecology clinic with pallor, tachycardia, recurrent syncopes when she was 20 weeks pregnant. In compliance with ethics standards, informed consent was obtained from the parents of the patient and is included in the hospital's clinical documents. Palpitations and syncopes had been present since the 12th week of gestation. Anemia and arrhythmia were detected, and she was referred to hematology after an erythrocyte transfusion. Personal history revealed that when she was 13 years old, she presented with abdominal pain, and splenomegaly during an upper respiratory tract infection and received an erythrocyte transfusion. Additionally, she had already received an erythrocyte transfusion due to anemia in the 12th week of gestation. The patient's parents were cousins, and the cousin of the patient was suffering from anemia requiring intermittent transfusions.

Physical examination revealed pallor, obliterated Traube's space, but spleen and liver size could not be evaluated due to pregnancy. Weight and height percentiles were 50 and 10 percentile, respectively. Abdominal ultrasonography confirmed hepatosplenomegaly. Laboratory studies of the patient before transfusion showed a hemoglobin (Hb) level of 7.7 g/dL, mean corpuscular volume (MCV) 65.0 fL, mean corpuscular Hb (MCH) 19.2 pg, and red blood cell distribution width (RDW) 28.2%. Complete blood count (CBC) values of the patient, spouse, child, and parents of the patient are shown in Table 1. The peripheral smear demonstrated severe hypochromia, anisopoikilocytosis, tear-drop shaped erythrocytes and microcytosis. Corrected reticulocyte count was 4.4%, serum ferritin level was 176.0 ng/mL, and bilirubin, lactate dehydrogenase (LDH) levels were normal. Hb H inclusions were demonstrated on the patient's peripheral blood with brilliant cresyl blue staining.

High performance liquid chromatography (HPLC) showed Hb A 94.5%, Hb H 4.0%, Hb A_2 1.5%, Hb F 0.0%. A multiplex polymerase chain reaction (PCR) analysis revealed $-\alpha^{3.7}/-(\alpha)^{20.5}$ confirming the Hb H diagnosis. The patient was put on a transfusion program during pregnancy in order to achieve a Hb level above 10.0 g/dL. The supplementation of folic acid was implemented. On the other hand, the cardiac evaluation revealed Wolff-Parkinson-White (WPW) syndrome, and she underwent radio frequency catheter ablation. Her spouse had average hematological values, peripheral smear, and globin electrophoresis, but genetic studies could not be studied. The pregnancy resulted in a full-term male weighing 3040 g. He is now 5 months old, and his hemogram values are shown in Table 1.

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Table 1. The complete blood count of the patient, her spouse, child, and patient's parents are presented.

Parameters	Patient	Mother	Father	Spouse	Child
Sex-age	F-16	F-37	M-45	M-19	M-5 months
Hb (g/dL)	7.7	12.7	16.2	15.9	10.3
RBC (10^{12}/L)	4.0	5.5	5.6	5.2	5.2
MCV (fL)	65.0	70.7	83.4	87.7	63.8
MCH (pg)	19.2	22.5	28.9	30.3	20.0
MCHC (g/dL)	29.5	31.8	34.6	34.6	31.4
RDW (%)	28.2	14.5	12.8	13.8	13.2
PCV (L/L)	0.25	0.37	0.47	0.46	0.33
Hb A (%)	94.5	NA	NA	96.7	NA
Hb A_2 (%)	1.5	NA	NA	2.8	NA
Hb F (%)	0.0	NA	NA	0.0	NA
Hb H (%)	4.0	NA	NA	0.0	NA

Hb: hemoglobin; RBC: red blood cell count; MCV: mean corpuscular volume; MCH: mean corpuscular Hb; MCHC: mean corpuscular Hb concentration; RDW: RBC distribution width; PCV: packed cell volume; NA: not available.

The incidence of α-thal disease is reported to be 0.25–4.10% in Turkey [3]. Although the incidence of α-thal is high, the relatively rare occurrence of Hb H disease may be due to inadequate reporting, insufficient awareness of the disease or the disease is usually asymptomatic without triggering factors such as infection, inflammation induced hemolysis or pregnancy as in our case [4]. In the majority of patients with Hb H disease, especially in deletional types, patients have normal growth, and their first transfusion usually is in the second decade, while jaundice is uncommon [4]. In our case, pregnancy worsened the anemia, and the anemia aggravated the arrhythmia.

According to the hemogram, the father of the patient carries a silent α-thal, and the mother is an α-thal trait carrier who had no genetic counseling. The patient was found to carry the $-\alpha^{3.7}/-(\alpha)^{20.5}$ deletions. The $-\alpha^{3.7}$ (rightward) deletion was reported to be most common, and $-(\alpha)^{20.5}$ deletion was the second most common in patients with Hb H disease in a study from Turkey [5]. The $-\alpha^{3.7}/-(\alpha)^{20.5}$ genotype was also reported as one of the most common genotypes in cohorts from Turkey [5,6]. Moreover, the $-\alpha^{3.7}$ and $-(\alpha)^{20.5}$ deletions were reported to be common in all Mediterranean populations [1]. Hematological parameters of the patients with a combination of deletional mutations have higher Hb and lower Hb H levels than patients who have nondeletional types of mutations [4,5,7]. The relatively mild presentation of the case highlights the milder phenotypic consequences of deletional α mutations *vs.* nondeletional α mutations.

It has previously been reported that pregnancies from mothers with Hb H disease might end in a preterm birth, low birth weight, and growth restriction of the developing fetus at higher risk [8]. As maternal anemia may hamper fetal growth by hypoxia, it was suggested to maintain Hb levels higher than 10.0 g/dL [9]. Prenatal screening of the fetus and on-demand transfusion therapy should be implemented according to fetal growth. Additionally, a lower limit of Hb level (10.0 g/dL) may be set up for pregnancies without close follow-up or symptomatic cases, as in the presented case.

The case highlights the need for universal prenatal screening for hemoglobinopathies in countries with high-risk populations. Screening for hemoglobinopathies might be performed at the neonatal period, school age, before marriage, or after marriage as part of family planning [10]. The premarital screening program has been widely available in Turkey since 2018. Unfortunately, the diagnosis of this case was missed before the pregnancy was diagnosed. All women can be screened for hemoglobinopathies as soon as a pregnancy is confirmed to minimize the incidence of new cases. Prenatal screening could be as simple as a CBC and Hb pattern analysis; however, further diagnostic tests are required for α-thalassemias or Hb variants.

In conclusion, the incidence of α-thal is high in Turkey [3]. The case points out deficiencies in prenatal screening. The authors recommend universal prenatal screening for hemoglobinopathies in countries with high-risk populations. Diagnosis of the Hb H disease would prevent unnecessary iron replacement therapies, possible thalassemic baby births, and restore pregnant women and fetal health.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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