
Homozygous β -Thalassemia (FCS8-AA) and Hereditary Spherocytosis in the Same Patient

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ABSTRACT

A three-year old Turkish girl having both homozygous β -thalassemia and hereditary spherocytosis and her family have been studied. The molecular defect causing thalassemia in the family was of the frame shift codon 8 (-AA) mutation type. The diagnosis of hereditary spherocytosis is based on osmotic fragility test in the patient and the family. However, the examination of erythrocyte membrane proteins has not been possible. β -thalassemia is in the heterozygous form in the mother, the father, and in two sisters. The mother, the father, and one of the sisters also have hereditary spherocytosis in addition to thalassemia. All those family members are asymptomatic. However, the patient who has frame shift codon 8 homozygosity along with hereditary spherocytosis presented with a severe form of hemolytic anemia.

Key Words: β thalassemia, Hereditary spherocytosis.

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INTRODUCTION

Hereditary spherocytosis (HS) is a hemolytic anemia characterized with the presence of spherocytes and increased osmotic fragility of erythrocytes. The disease has a heterogeneity of presentation driving from the different mo-

lecular defects in the membrane proteins (spektrin, ankyrin, bands 4.2 and 3) of the erythrocyte. As a consequence, patients may be symptomatic even in the neonatal period, and asymptomatic adult cases can also be seen^[1-3]. β -thalassemia (β -thal) on the other hand, is a severe anemia which, as a consequ-

ence of a pathogenetic defect in the β -globin gene, is both hypochromic due to decreased or absent synthesis of the β -globin chain and hemolytic due to the effect of uncoupled α chains. It constitutes a major health problem in Turkey^[4-6].

The spontaneous occurrence of HS and β -thal in the same family is a rare event. There are only seven families in which both disease have been reported, and all of the cases in those families are heterozygote for β -thal^[2,7,8]. Further, during our studies since 1970, our group diagnosed only two families with this combinational defect among 76 HS families^[9,10].

The aim of the study is to present five members of one family with hereditary spherocytosis in association with beta thalassemia.

CASE REPORT

We report a three year-old girl diagnosed as hereditary spherocytosis and homozygous beta thalassemia with the Frame shift codon 8 (-AA) mutation who was brought from Elbistan, Turkey with complaints of fatigue, pallor and excessive sweating. To our knowledge, no such case has been previously reported. She had been affected at the age of 20 day, and that she had developed a prominent pallor, and failed to gain weight after three months of age. She had not managed to sit at the expected time, and has not managed to walk yet. She had not been favorably affected by the iron preparations previously prescribed and she had transfusion twice. In the physical examination, her weight, height, and head circumference were measured as 10300 g, 86 cm, and 50 cm, respectively. She was fatigued and pale. She had an apex beat of 124/min. Her liver was 1.5 cm below the right costal margin. The spleen was not palpated, but dullness was obtained over the traube by percussion. Because of severe anemia (her hemoglobin concentration was 4.9 g/dL) and typical facial features, β -thalassemia major was suspected, and her hemoglobin electrophoresis was performed.

In the hemoglobin electrophoresis, HbA₂ was 1.7%, and Hb F was 54.5%. The HbA₂ ratios of her father and her mother was 7% and 5.9% respectively. Although a diagnosis of β -thalassemia major was established, the presence of spherocytes along with hypochromic erythrocytes and her mean corpuscular volume (MCV) which was 76.7 fl led us to consider the co-presence of spherocytosis. Osmotic fragility test was performed.

In osmotic fragility testing, 5% and 29% hemolysis were detected before and after incubation in 0.6% and 0.9% saline solutions respectively in the patient (Figure 1a) and her parents (Figure 1b, 1c).

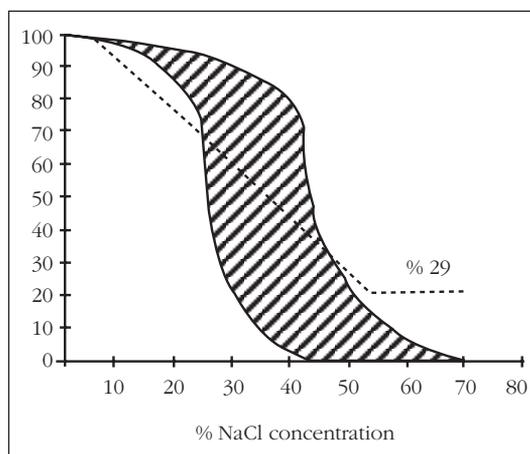


Figure 1a. Incubated red cell Osmotic fragility curves of the patient.

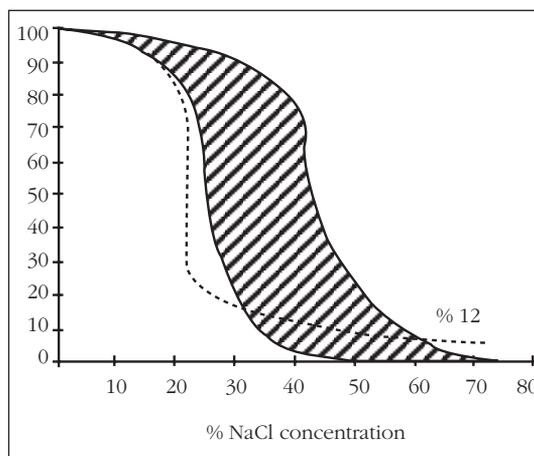


Figure 1b. Incubated red cell Osmotic fragility curves of the father.

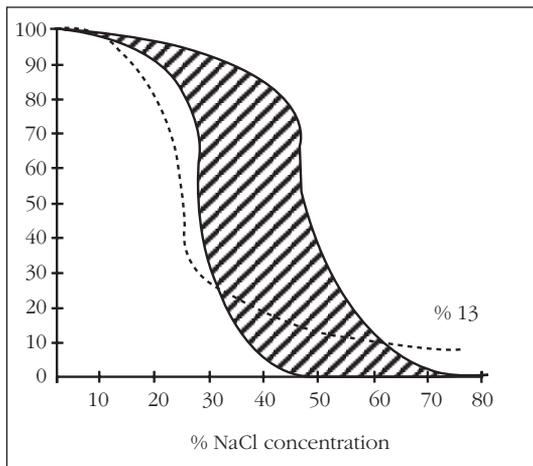


Figure 1c. Incubated red cell Osmotic fragility curves of the mother.

The other laboratory values of the patient were as follows. Serum iron: 210 μ /dL. Unsaturated iron binding capacity: 0. Transferin saturation: 100%. Coomb's test negative. Total bilirubin: 1.50 mg/dL. Direct bilirubin: 0.46 mg/dL. LDH: 477 U/L.

AST: 27 U/L. ALT: 15 U/L. BUN: 8 mg/dL. Creatinine: 0.3 mg/dL. Calcium: 9.8 mg/dL. Inorganic phosphorus: 4 mg/dL. Alkaline phosphatase: 131 U/L. Ferritin: 256 ng/dL. erythrocyte sedimentation rate: 12 mm/h. The hematological values of the patients and her family members that have been studied are given in the table (Table 1). The mother and the father were relatives, one parent of each being sibs. The uncle was said to have

been splenectomized on account of anemia, and then recovered (Figure 2).

METHODS

Hematological data were obtained from a Counter Model CT Reticulocyte counts were made after cresyl blue staining. HbA2 and Hb F levels were estimated in electrophoresis on cellulose acetate (Helena Lab. USA). Osmotic fragility curves were drawn using the method previously described. The erythrocyte fragility was determined before and after incubation^[9]. The mutation analyses for β -thalassemia were done according to previously defined methods^[6]. We did not have the facility to perform the analysis of the skeletal proteins of the erythrocyte membrane in the patient and in the family.

DISCUSSION

In result, our patient has homozygous FSC 8(-AA) β -thalassemia and hereditary spherocytosis. Both her mother and father are heterozygous β -thalassemia trait. Her younger sister has β -thalassemia trait, hereditary spherocytosis, and iron deficiency anemia.

The mutual presence in the same patient of two hereditary hemolytic anemias that develop due to intrinsic defects of erythrocytes is not a common occurrence. Moreover, to our knowledge, there are no previously reported cases of the homozygous form of β -thalassemia occurring with HS and following this severe a course other than the patient we report here. However, co-occurrence of HS with thalassemia trait has been reported^[2,7,8].

Table 1. Hematological parameters and β -thalassemia mutations of the family

	Hb g/dL	Retic. %	MCV fL	MCHC pg	MCHC	RDW	HbA2	HbF %	OFT %	β -thal mutation
Father	11.9	0.5	60.9	29.5	29	16.3	7.0	2↓	+ (12)	FSC8 (-AA)
Mother	9.1	1.9	58.2	29.5	17	18.7	5.9	2↓	+ (13)	FSC8 (-AA)
Sister (9 y)	10.2	1.0	57	-	18.1	-	5.6	-	- (0)	FSC8 (-AA)
Patient (3 y)	4.9	2.87	76.7	33.8	30	26	1.7	54.5	+ (29)	FSC8/FSC8
Sister (1.5 y)	8.4	1.2	47	-	30	14.3	4.8	5.3	+ (4)	FSC8 + Iron deficiency anemia

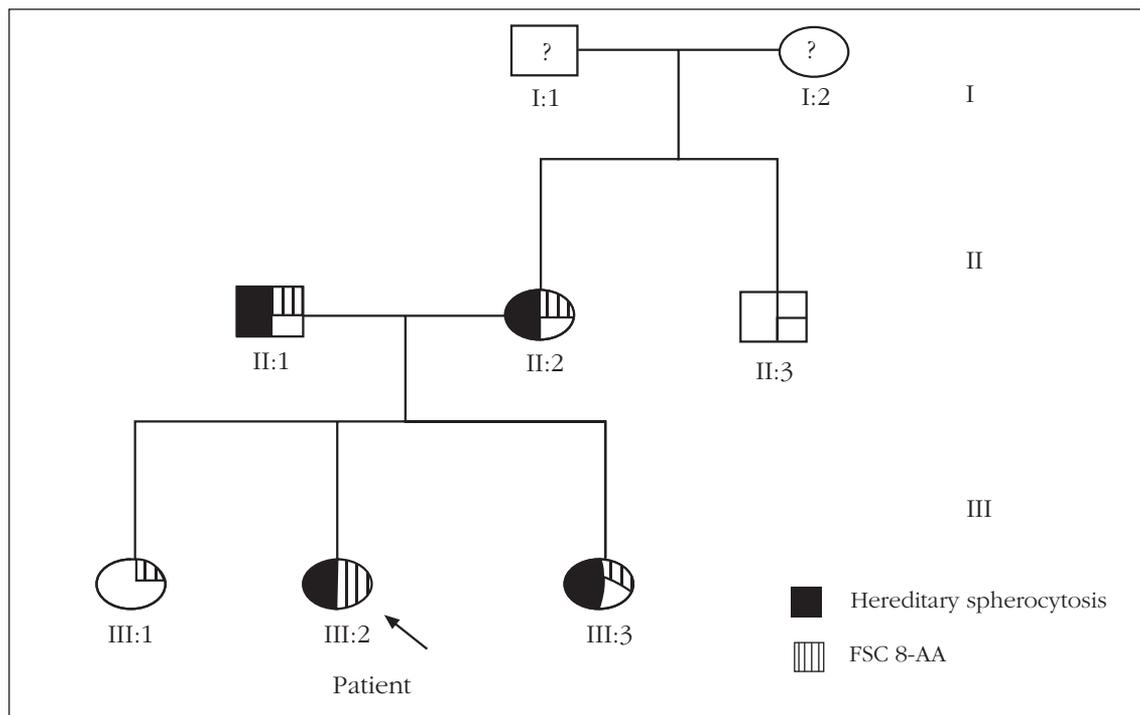


Figure 2. Pedigree of the patient.

Thalassemia and HS have typical features that oppose each other. Thalassemic erythrocytes have increased surface/volume ratio. On the other hand, in HS, erythrocytes have decreased surface/volume ratio and high hemoglobin content. This way, one abnormality has been thought to compensate for the other, but there are also studies which suggest that this mechanism can only bring about changes in the osmotic fragility curve, and that it would not have much effect on the clinical presentation^[8].

There was no phenotypic pathology other than a marked increase in erythrocyte fragility as shown by OFT and a microcytic anemia in the mother, father and sister. Heterozygote state of β -thal that did not effect the clinical symptoms.

In our patient who has homozygous β -thalassemia, it is not easy to think of this disease process as the only factor responsible for the severity of the clinical course, because her high MCHC (33.8 g/dL) and the high-for-tha-

lassemia MCV (76.1fL) values and her high reticulocyte count (2.8%) indicates that the HS is also operative (Table 1).

The osmotic fragility curve of our patient was markedly diagnostic especially after incubation. The evaluation of osmotic fragility curves is sufficient to diagnose HS. However, in order to determine the severity of the disease process, the defect in the membrane proteins of the erythrocyte must also be determined^[13]. Unfortunately, we have not yet undertaken such a work up regarding those membrane proteins.

Our patient's younger sister shows an interesting presentation. Here, there is iron deficiency occurring simultaneously with two hemolytic anemias, HS and β -thalassemia trait. Although relative iron deficiency secondary to increase in erythropoiesis can occur^[10], it is not feasible for us to speculate on this.

In conclusion, in this patient whom had been diagnosed to have β -thalassemia major,

HS was suspected on the information obtained by such simple laboratory procedures as the examination of blood film, MCV and MCHC. Then, the co-occurrence of HS was verified by osmotic fragility testing and the examination of the other members of the patient's family. With this occasion, we find it appropriate to call attention to the fact that the careful examination of the blood film and blood indices are tools that are still valuable, in our day and age, in the differential diagnosis of anemia.

Homozygous β -thalassemia patients carrying the FCS8(AA) mutation shows the intermedia clinical course^[12]. Clinical severity of our patient indicates that the coexisting of HS is an aggravating factor.

Further analysis of membrane proteins will probably give more information on the course of this disease state.

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