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We have studied 39 patients doubly heterozygous for sickle cell/β-thalassemia, 12 with sickle cell/β^0-thalassemia and 27 with sickle cell/β^+-thalassemia. Generally, sickle cell/β^0-thalassemia is considered more severe than sickle cell/β^+-thalassemia. In our study, however, clinical complications in the group with sickle cell/β^+-thalassemia were seen almost as frequently as in the group with sickle cell/β^0-thalassemia. A wide variety of clinical manifestations were seen in both groups of patients. (Henry Ford Hosp Med J 1986;34:282-4)

The double heterozygous condition, sickle cell/β-thalassemia, is seen in whites (predominantly Greeks and Italians) in the Mediterranean area of southern Europe, and mainly in blacks in the United States (1-6). The disease is known to manifest a variety of clinical symptoms, particularly vaso-occlusive crises as well as other, more chronic complications noted later. Clinically, the cases may range from mild to severe, the latter resembling sickle cell anemia (SS). Sickle cell/β-thalassemia has been subdivided into 1) sickle cell/β^+-thalassemia in which there is impaired but still significant β-chain synthesis, and 2) sickle cell/β^0-thalassemia in which there is no β-chain production. The former condition is more common in blacks and is considered clinically milder than the latter condition (4,6,7). However, the clinical reports regarding these two subgroups are relatively scarce. Furthermore, in our practice we have seen patients with sickle cell/β^+-thalassemia suffering from several complications even though it is considered a milder disease. Our experience with both subtypes of sickle cell/β-thalassemia has been fairly extensive and is the basis for this report, which compares the two subtypes with respect to clinical and hematologic manifestations.

Materials and Methods

Thirty-nine patients with sickle cell/β-thalassemia were seen at Henry Ford Hospital during the past ten years.

In general, patients with microcytic red cells, a predominance of hemoglobin S, no hemoglobin A, variably increased hemoglobin A_2, and variably increased hemoglobin F were considered to have sickle cell/β^0-thalassemia. Patients with microcytic red cells, a predominance of hemoglobin S, a minor component of hemoglobin A (in the absence of recent blood transfusion), variably increased hemoglobin A_2, and variably increased hemoglobin F were considered to have sickle cell/β^+-thalassemia. Sickle cell/β^0-thalassemia was distinguished from sickle cell anemia by the presence of microcytosis and elevated hemoglobin A_2 levels. In some cases confirmation was obtained by family studies. Sickle cell/β^0-thalassemia was distinguished from double heterozygocity for hemoglobin S and hereditary persistence of fetal hemoglobin on clinical grounds as well as by the presence of microcytosis and elevated hemoglobin A_2 levels. Sickle cell/β^0-thalassemia was differentiated from double heterozygocity for hemoglobin S and hemoglobin Lepore by acid citrate agar electrophoresis.

All the patients' charts were reviewed. Complete blood counts were determined by a Coulter Model S and S Plus electronic cell counters. Hemoglobin analysis was done by cellulose acetate electrophoresis using TRIS-EDTA acetate buffer at pH 9.2 and citrate agar electrophoresis with sodium citric acid buffer at pH 6.2. Hemoglobin F was also measured by alkaline denaturation. Hemoglobin A_2 was determined by column chromatography. Student's *t* test and the Fisher exact test were used for comparison of the data.

Results

The patients' ages ranged from 1 to 81 years, with a mean of 28 years. Twelve patients were younger than 18 years of age. Of the 39 patients, 22 were women and 17 were men. There were 36 blacks and three whites.

Hematologic data

The hemoglobin ranged from 5.7 to 15.1 g/dL, with a mean of 10.5 g/dL. The mean corpuscular volume ranged from 63 to 80.7 U^3, with a mean of 72.3 U^3. The average mean corpuscular hemoglobin concentration was 32.6%. The reticulocyte count was determined in 26 patients; the count ranged from 0.8% to 30.5%, and the mean was 6.4%.

Twelve patients had no hemoglobin A and were considered to have sickle cell/β^0-thalassemia. The remaining 27 patients had hemoglobin A ranging from 8.7% to 26.8%, with a mean of

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Table 1
Hematological Data

	Sickle Cell/β^0-Thalassemia			Sickle Cell/β^+-Thalassemia			
	No.	Mean	Range	No.	Mean	Range	P-value
Hemoglobin (g/dL)	12	8.7	5.7-10.9	27	11.3	8.4-15.1	0.01
Reticulocyte (%)	10	8.7	2.0-30.5	16	4.9	0.8-25.0	0.01
Hemoglobin S (%)	12	83.7	74.0-95.7	27	67.8	46.2-83.4	0.01
Hemoglobin A (%)	12	0	0	27	18.8	8.7-26.8	—
Hemoglobin F (%)	12	11.7	0.2-22.3	27	8.3	0.8-27.7	NS
Hemoglobin A_2 (%)	12	5.0	3.4-6.9	27	4.9	2.1-7.2	NS
MCV (U^3)	12	72.2		27	69.6		NS
MCHC (%)	12	31.8		27	31.4		NS
Bilirubin (mg%)	10	2.1	0.7-3.1	17	1.7	0.3-11.0	—

NS = not significant.

18.8%. The hemoglobin A_2 ranged from 2.1% to 7.2%, with a mean of 4.9%. The hemoglobin F ranged from 0.2% to 27.7%, with a mean of 9.3%. The hemoglobin S ranged from 46.2% to 95.7%, with a mean of 72.7%.

Total bilirubin was available in 27 patients. It ranged from 0.3 to 11.0 mg%, with a mean of 1.9 mg%.

Clinical findings

Thirty-two patients had painful episodes, seven had hepatomegaly, one had a leg ulcer, 18 had joint pain, four had cardiomegaly, and four had avascular necrosis of bone. Three of the four patients with avascular necrosis of bone had involvement of the hip. Fifteen patients had splenomegaly, and two patients had undergone splenectomy.

Other complications observed included two patients with dactylitis (periostitis of the small bones of the hands and feet), three patients with thrombophlebitis of the leg, three patients with cholelithiasis requiring cholecystectomy, and three patients with retinal hemorrhages and detachments. In addition, sporadic pneumonia, upper respiratory infection, and urinary tract infection were observed in some patients. Two patients with sickle cell/β^0-thalassemia died at 33 and 38 years of age, respectively. The death of the 33-year-old, a black woman, was due to thrombophlebitis and congestive heart failure associated with severe chronic anemia requiring multiple transfusions. The 38-year-old, also a black woman, died of congestive heart failure associated with anemia. A 19-year-old black man with sickle cell/β^0-thalassemia is doing poorly with neurologic impairment due to a stroke, poor vision, hematuria, and hemoptysis. A 26-year-old woman with sickle cell/β^+-thalassemia had autoimmune hemolytic anemia and iliofemoral thrombosis.

Ten of the 39 patients had a history of transfusions. Nine had received transfusions for anemia, and one patient had received a transfusion in preparation for hernia repair surgery. Five of the nine who received transfusions for anemia were β^0-type and four were β^+-type. No patient received a transfusion in the period preceding hemoglobin electrophoretic study.

Sickle cell/β^0-thalassemia versus sickle cell/β^+-thalassemia

As previously described, 12 patients had sickle cell/β^0-thalassemia and 27 had sickle cell/β^+-thalassemia. Laboratory and clinical results in these two groups are compared in Tables 1 and 2. There were statistically significant differences in certain laboratory results. The mean hemoglobin level was lower and the mean level of hemoglobin S and mean reticulocyte count were higher in patients with sickle cell/β^0-thalassemia. There was no significant difference in the frequency of different clinical manifestations except for cardiomegaly, which was more frequent in β^0-thalassemia.

Discussion

In our study sickle cell/β^+-thalassemia was more common than sickle cell/β^0-thalassemia. These findings are similar to those reported from Jamaica (4,7), probably because most of our patients were black, and blacks tend to carry the β^+ gene more frequently than the β^0 gene. A variety of clinical manifestations were observed in both groups of patients, including painful episodes, splenomegaly, joint pain with or without effusion, hepatomegaly, avascular necrosis of bone, cardiomegaly, and leg ulcers (4,6,8,9). When the group of patients with sickle cell/β^+-thalassemia was compared to the group with sickle cell/β^0-thalassemia in terms of incidence of the different clinical manifestations, there was no statistically significant difference between the two groups except for cardiomegaly. Cardiomegaly was more frequent in the group with sickle cell/β^0-thalassemia. Serjeant and Serjeant observed that the clinical course was more severe in patients with sickle cell/β^0-thalassemia than in patients with sickle cell/β^+-thalassemia (7). Since our statistical comparison was based on the incidence of the various complications, we can neither discount nor support the conclusions of Serjeant and Serjeant. After seeing early deaths in two patients and severe clinical disease in a third patient with sickle cell/β^0-thalassemia, we certainly recognize that sickle cell/β^0-thalassemia can be a severe disease in some patients. What we wish to emphasize is that frequent complications also can occur in patients with sickle cell/β^+-thalassemia.

When laboratory data for the two groups were compared, several statistically significant differences were noted: the mean hemoglobin S level and the reticulocyte count were higher and the mean hemoglobin level was lower in the group with sickle cell/β^0-thalassemia. Our series included 12 younger patients, seven with sickle cell/β^+-thalassemia and five with sickle

Table 2
Clinical Manifestations

	Sickle Cell/β^0-Thalassemia	Sickle Cell/β^+-Thalassemia	P-value
Age			
No./Mean	12/25	27/30	
Range (years)	8-52	1-81	
Sex			
Males	3	14	
Females	9	13	
Race			
Blacks	12	24	
Whites	0	3	
Hepatomegaly	3 (25%)	4 (15%)	NS
Splenomegaly	5 (42%)	10 (37%)	NS
Joint pain	7 (58%)	11 (41%)	NS
Cardiomegaly	4 (33%)	0 (0%)	0.02
Painful episodes	12 (100%)	20 (74%)	NS
Avascular necrosis of bone	0 (0%)	4 (15%)	NS
Cholecystectomy, gallstone	1	2	
Thrombophlebitis	2	1	
Dactylitis	1	1	
Retinopathy	1	2	
Other			
Died at young age	2	0	
Transfusion	5	5*	

*One out of five was exchange transfusion.
NS = not significant.

cell/β^0-thalassemia. When considering the influence that age might have had on the comparative analysis, ie, that more younger children in one group than the other may have affected the results of the comparison between the two groups of patients, our statistical analysis revealed that the age factor did not appear to influence the comparison.

A fairly wide range of clinical complications was observed in patients with sickle cell/β^+-thalassemia and in those with sickle cell/β^0-thalassemia. Clinical complications were almost as frequent in patients with sickle cell/β^+-thalassemia as in those with sickle cell/β^0-thalassemia. With the exception of cardiomegaly, which was observed more frequently in the sickle cell/β^0-thalassemia group, there was no statistically significant difference between the two groups with respect to clinical complications. Regarding the laboratory findings, patients with sickle cell/β^0-thalassemia tended to have lower hemoglobins, higher levels of hemoglobin S, and higher reticulocyte counts than patients with sickle cell/β^+-thalassemia.

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