Sickle Cell Syndromes. III. Silent-Carrier α -Thalassemia in Combination with Hemoglobin S and Hemoglobin C

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Summary

Silent carrier α -thalassemia was identified in two individuals, one with sickle-cell trait and the other hemoglobin (Hb) C trait. Both are parents of a child with characteristic hematologic features of the Hb SC- α thalassemia syndrome, including microcytosis and an unbalanced pattern of globin synthesis. In contrast to the typical findings that accompany heterozygous Hb S or Hb C with concomitant α -thalassemia trait, neither of the parents had microcytosis nor a percent of the abnormal hemoglobin in their erythrocytes that was below the normal range. In both, however, globin synthesis of peripheral blood reticulocytes was unbalanced, consistent with mild α -thalassemia. These findings suggest that the α -thalassemia silent carrier may be hematologically indistinguishable from the nonthalassemic individual, even when hemoglobin S or C are present.

Speculation

These findings provide additional evidence that the genetic pattern of α -thalassemia in American blacks is probably similar to that previously characterized in Far-Eastern populations, in spite of the clear differences in the clinical and hematologic expression of these disorders in the two populations.

Syndromes representing the coexistence of α -thalassemia trait and the heterozygous forms of Hb S or Hb C have been recognized with considerable frequency in the American black population (3, 9, 17, 19). The characteristic hematologic expression of these syndromes includes significant microcytosis as well as less than the usual percent of the abnormal hemoglobin in the blood. In this report, a milder form of α -thalassemia trait is described that was present in combination with heterozygous Hb S and Hb C. Erythrocyte indices of the affected individuals as well as the percents of Hb S and Hb C in their blood were within the normal range of Hb AS and Hb AC individuals.

METHODS

Hematologic measurements were made with a Coulter Model S electronic cell counter that was standardized daily using a commercial standard. Other determinations were performed by standard methods (2). Informed consent was obtained for all of the clinical studies.

Hemoglobins S and C were identified by electrophoresis on cellulose acetate in tris-EDTA-borate buffer, pH 8.6 (15), in agar gel at pH 6.2 (12), and by solubility testing (4). Hemoglobin quantitation was performed by elution of the individual hemoglobin fractions after cellulose acetate electrophoresis (6).

Procedures for studies of incorporation of L-leucine- 14 C into globin chains by peripheral blood reticulocytes were as previously described (8). Ratios of α /non α chain synthesis were calculated

from chromatographic fractions corresponding to each of the globin chains.

CASE REPORT AND RESULTS

E. H., a 9-yr-old black child, was referred to the Children's Memorial Hospital at age 5 after a screening test that suggested the presence of a Hb abnormality. The child was born after a full term pregnancy that was complicated by maternal anemia. He had been in good health and had a normal pattern of growth and development. A physical examination revealed no abnormality.

A Hb electrophoresis determination demonstrated the presence of Hbs S and C in approximately equal quantities. The child was mildly anemic and had an elevated reticulocyte count, both consistent with Hb SC disease. A stained smear of his blood disclosed many of the typical morphologic features of Hb SC erythrocytes; in addition, however, the erythrocytes appeared strikingly microcytic, and a majority of the cells were thin-appearing target forms. These morphologic changes were reflected in substantially reduced MCV and MCH indices (Table 1). Iron deficiency was excluded as a cause for the microcytosis by findings of normal levels of serum iron, iron saturation, and serum ferritin. Because of the similarity of the hematologic features of this patient to those of a previously described child with Hb SC and concomitant α -thalassemia trait (5), a globin synthesis study was performed using peripheral blood from the child (Fig. 1). The significantly reduced α /non α synthesis ratio of 0.69 that was obtained was also similar to that of the previously described patient (5) and served to confirm this diagnosis.

Hematologic and hemoglobin studies were also carried out with blood samples obtained from the child's parents (Table 1). The mother was found to have sickle-cell trait and the father Hb C trait. Neither parent was observed to be anemic, and although both had relatively low erythrocyte MCV values all of their red cell indices were well within the range of normal values (Table 1). Measurements of Hb S and Hb C in blood samples from the parents (Table 1) also demonstrated percents of these hemoglobins that were within the range that have been observed in heterozygous individuals (Table 1). Thus, both by hematologic criteria and hemoglobin measurements, neither of the parents were distinguishable from individuals with usual forms of sickle-cell trait and Hb C trait. The α /non α globin synthesis ratios, however, (Table 1) were significantly reduced in blood samples from both parents. The degree of α /non α synthesis imbalance was intermediate between that found in Hb S or Hb C trait and in sickle cell trait with concomitant α -thalassemia trait (Table 1) suggesting that both parents have a very mild form of α -thalassemia.

DISCUSSION

The current understanding of the α -thalassemia syndromes, including their hematologic expression and mode of inheritance,

Table 1. Hematologic and hemoglobin findings of the patient and his parents

Subject	Hb (g/dl)	PCV (%)	MCV (fl)	MCH (pg)	Reticulo-cytes (%)	Serum			Hb A ₂ (%)	Hb F (%)	Hb S (%)	Hb C (%)	L-leu- ¹⁴ C incorporation		
						iron (μg/dl)	iron saturation (%)	serum ferritin (ng/ml)					α/β ^A	α/β ^S or β ^C	α/nonα
Proband	10.8	33.4	56	18.2	3.8	82	22.0	46		1.7	51.8	46.5	β ^S /β ^C = 0.93		0.69
Father	16.8	49.4	82	27.9	0.9	74	22.8	120		1.9		38.1	1.35	2.13	0.76
Mother	13.9	40.4	81	27.6	1.4	98	31.4	174	3.4	1.5	32.7		1.20	2.48	0.75
Controls															
Sickle-cell trait			88.4	28.4							35.4		1.86	3.02	1.07
			±5.2	±1.9							±3.0		±0.33	±0.28	±0.12
Hb C trait			84.0	27.3								38.4	1.89	2.53	1.01
			±3.4	±1.5								±4.2	±0.26	±0.19	±0.12
Sickle-cell trait with α-thal trait ¹			69.1	22.4							25.8		1.10	3.05	0.65
			±2.5	±1.1							±1.4		±0.23	±0.48	±0.10

¹ These subjects included eight individuals with Hb AS and α-thalassemia trait, most of whom have been described in previous reports (5, 7).

Fig. 1. Incorporation of L-leucine-¹⁴C into globin chains by peripheral blood reticulocytes. A: the child (Hb SC); B: the mother (Hb AS); C: the father (Hb AC).

has been derived mainly from studies of Far Eastern populations in which these disorders occur with high frequency (10, 20). Four distinct forms of α-thalassemia have been identified that include, in order of increasing severity, the α-thalassemia silent carrier phenotype, α-thalassemia trait, hemoglobin H disease, and the hydrops fetalis form of α-thalassemia. Based on evidence that the α chain structural genes in most individuals exist on the chromo-

somes as a linked pair of apparently identical loci (11) these α-thalassemia syndromes have been interpreted to represent deletion or replacement of normal α chain genes by 1, 2, 3, or 4 α-thalassemia genes, respectively.

The expression of α-thalassemia in American black populations differs from that seen in the Far East mainly by a generally milder picture in blacks, both in the hematologic expression and in the degree of imbalance of α/β chain synthesis (16, 18); the hydrops fetalis form of α-thalassemia has not been described in blacks. In an effort to account for these differences, it has been postulated that the form of α-thalassemia that occurs in blacks may represent a milder α-thalassemia gene and possibly as well a different pattern of genetic transmission such that its homozygous expression might produce disease of lesser severity (5, 16, 18). As an alternative explanation, it was suggested (11) that α-thalassemia in blacks may follow a genetic pattern similar to that of Asian populations, but that the corresponding genes might exist predominantly in a linkage pattern in which an α-thalassemia gene occurs on a chromosome also having a normal α chain structural gene. With such a distribution severe forms of α-thalassemia would not occur in this racial group. At variance with this concept is the recent demonstration (13, 14) of severe α-thalassemia genes that appear to be occupying both of the linked loci of a single chromosome, in two black Americans. The frequency of this type of abnormality in the American black population is unknown, however, and it may be of rare occurrence.

A recent report by Altay *et al.* (1) describes observations from a group of black American children in whom elevated levels of Hb Barts (γ₄) were present at birth. The findings in these children and in members of their families suggested that α-thalassemia trait could be distinguished from the silent carrier phenotype in this population, a finding that further supports the genetic parallelism between α-thalassemia in Asians and that occurring in American blacks. Another recent report by Huisman (9) describes a group of black Americans with α-thalassemia who also were heterozygotes for various hemoglobin β-chain structural abnormalities. A trimodal distribution of the percent of the β-chain variants was found in these individuals, with the three groups appearing to correspond to the nonthalassemic state, the silent carrier form of α-thalassemia, and α-thalassemia trait. In the subjects with sickle-cell trait or Hb C trait who were included in this study, those with the lowest percent of Hb S or Hb C also demonstrated hematologic and globin synthesis findings consistent with the α-thalassemia trait syndrome. Those in the intermediate group had relatively reduced erythrocyte indices, but the values showed considerable overlap with those of apparently nonthalassemic subjects. These findings were interpreted to represent the α-thalassemia silent carrier phenotype.

The patient described in the present report demonstrated characteristic features of the Hb SC-α-thalassemia trait syndrome (5) yet neither of his parents demonstrated any hematologic abnormality apart from findings related to their variant hemoglobins.

Fig. 2. Hemoglobin genotype of the child and his parents.

The assumed genotype of the members of this family is illustrated in Figure 2.

Significantly, the location of the α -thalassemia loci on separate chromosomes in this child contrasts with that of the previously described patient with Hb SC- α -thalassemia trait in whom the genetic data indicate that the α -thalassemia determinants existed on a single chromosome. In both cases, however, the hematologic disorders were expressed in a very similar manner. These findings lend further support to the previous evidence that the four-gene α -chain locus hypothesis, with its implications for α -thalassemia genetics, appears to provide a valid model for the α -thalassemia syndromes of blacks.

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