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THE CLINICAL SEVERITY OF HEMOGLOBIN S / BLACK ($A\gamma\delta\beta$)⁰-THALASSEMIA

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Abstract

Hemoglobin S/Black ($A\gamma\delta\beta$)⁰-thalassemia is a rare sickle cell disease (SCD) variant. Based on limited descriptions in the literature, the disease is reported as a mild microcytic anemia with an uncomplicated course. We report the clinical and laboratory data of nine patients whose diagnoses were confirmed by DNA-based techniques. Despite having mild anemia and high fetal hemoglobin level post-infancy, these patients developed many of the classic complications of SCD, including vaso-occlusive crisis, acute chest syndrome, avascular necrosis, and cholelithiasis. Based on these findings, we recommend that patients with this rare disorder receive specialized hematology care according to SCD guidelines.

Keywords

Sickle cell disease; sickle cell anemia; thalassemia; sickle gamma delta beta thalassemia; $G\gamma(A\gamma\delta\beta)$ ⁰-thalassemia

INTRODUCTION

A-gamma delta beta thalassemia is a rare form of thalassemia resulting from large deletions, including the $A\gamma$, δ and β globin genes. There are at least 11 different forms reported,[1] one of which, the Black($A\gamma\delta\beta$)⁰-thalassemia, may occur in association with sickle hemoglobin (HbS). Laboratory and clinical characterizations of Black($A\gamma\delta\beta$)⁰-thalassemia (homozygous

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and compound heterozygous) have been reported, yet little information exists for the compound heterozygotes with HbS, a rare variant of sickle cell disease (SCD) that is considered to have a mild clinical course as previously reported in only 7 individuals.[2] HbS/Black($\text{A}\gamma\delta\beta$)⁰-thalassemia occurs primarily in persons of African ancestry and is associated with high fetal hemoglobin (HbF) level, mild anemia, and slight microcytosis with hypochromia. Herein we describe the hematological and clinical course of nine children with HbS/Black($\text{A}\gamma\delta\beta$)⁰-thalassemia who, contrary to the existing literature, developed many of the complications of SCD.

CASE DESCRIPTIONS

With institutional review board approval, a search of clinical databases of three SCD programs between 2000 and 2014 identified nine patients with HbS/Black($\text{A}\gamma\delta\beta$)⁰-thalassemia. Each patient underwent hemoglobin analysis by Bio-Rad Variant II high performance liquid chromatography and confirmation by gap-PCR test and nucleotide sequencing in the Hemoglobin Diagnostic Reference Laboratory (Boston Medical Center). Six of the nine patients (P1, P4, P5, P6, P7, P8) were identified through newborn screening (HbFS and absent HbA, Table 1). The remaining patients were referred in their second decade of life, following identification through sickle cell trait screening (P2 and P3), and referral by a rheumatologist (P9) who noted hip pain and mild microcytic anemia not attributed to a rheumatologic disorder. These nine patients had in common persistently elevated HbF levels (>20% after age 1), partially compensated hemolytic anemia, and all underwent comprehensive hemoglobinopathy testing to investigate the etiology of HbF elevation. Molecular testing identified a deletion of 35.8 kb with the 5' breakpoint in IVSII of the $\text{A}\gamma$ globin gene and the 3' breakpoint at the L1 repeat downstream of the β globin gene (Supplemental Figure S1).

HbS/Black($\text{A}\gamma\delta\beta$)⁰-thalassemia children had mild microcytic anemia, reticulocytosis, and hyperbilirubinemia (Table 1). Peripheral blood smear disclosed anisocytosis, poikilocytosis, microcytosis, target cells, and rare sickled forms (Supplemental Figure S2). Prophylactic penicillin was provided to all diagnosed in the newborn period and most continued this until age 5.

P1 had dactylitis at age 7 months. No other vaso-occlusive crisis (VOC) events were recorded at the time of last follow-up, at age 13. Analysis by flow cytometry showed 94.8% HbF positive cells (Supplemental Figure S3).

P2 and P3 were prematurely-born twins who were referred at age 17 years, after sickle cell screening at a health fair. They had multiple hospital visits for management of severe lower extremity pain in the absence of trauma or other inciting events, both before and after diagnosis. These episodes required intravenous hydration and analgesia. P3 underwent cholecystectomy for symptomatic cholelithiasis at age 19.

Patient 4 had dactylitis at age 2. He required hospitalization twice between the ages of 2 and 3 for acute chest syndrome (ACS; fever, pain, cough, and a new pulmonary infiltrate), without requirement for supplemental oxygen. Therapy with hydroxyurea was initiated with

subsequent improvement of VOC symptoms. Qualitative HbF analysis by flow cytometry showed 91.7% HbF positive cells (Supplemental Figure S3).

P5 had no sickle related complications at last follow-up at age 4.

P6 had mild splenomegaly, multiple episodes of VOC by age 11, and recurrent episodes of abdominal pain (without documentation of cholelithiasis) concurrent with pain in extremities.

P7 had frequent complains of abdominal pain, which after extensive gastrointestinal evaluation, were attributed to constipation. No VOC events were recorded by his last follow-up at age 4.

P8 was admitted for fever and first episode of leg pain at age 7; magnetic resonance imaging (MRI) was suggestive of osteomyelitis. His symptoms improved within 4 days of antibiotics, recurred upon premature discontinuation, but resolved when antimicrobials were resumed.

By age 9, P9 had splenomegaly and multiple admissions for severe recurrent pain in the upper and lower extremities and back, consistent with VOC. MRI revealed multifocal avascular necrosis affecting both hips and right shoulder. Hydroxyurea was initiated resulting in fewer VOC episodes.

During the period of this analysis (60.7 patient-years), SCD-related complications occurred in seven out of nine patients. These complications included VOC, dactylitis, cholelithiasis, osteonecrosis, ACS, and osteomyelitis. There were no instances of splenic sequestration, stroke or sepsis. No erythrocyte transfusions were required for SCD-related complications. Additionally, normal transcranial Doppler ultrasound velocities were noted in three patients (P1, P4, P5), and three had obstructive sleep apnea (P5, P8, P9). Laboratory values were plotted as a function of age; HbF declined after birth, but overall remained at approximately 20%, mean corpuscular volume (MCV) remained stable, and Hb concentration increased slightly with age (primarily driven by teenagers P2 and P3 who entered the cohort at age 17) (Figure 1).

DISCUSSION

The compound heterozygous HbS/Black($\text{A}\gamma\delta\beta$)⁰-thalassemia produces a rare SCD variant that, until this date, had only been described in 7 cases worldwide.[2] Here we describe the clinical course of nine patients from birth to age 24 with HbS/Black($\text{A}\gamma\delta\beta$)⁰-thalassemia whose molecular characterization shows distinct beta globin locus breakpoints from the benign compound heterozygous HbS and hereditary persistence of fetal hemoglobin (HbS/HPFH), but also exhibits high HbF levels (Supplemental Figure S1). Their course was not always as benign as reported in the literature or generally assumed, with SCD-related complications occurring from infancy into young adulthood.

HbS/Black($\text{A}\gamma\delta\beta$)⁰-thalassemia was described in 1985, when restriction enzyme analysis was used to study members of 10 families with conditions considered to be $\text{G}\gamma(\delta\beta)$ ⁰-thalassemia or $\text{G}\gamma(\delta\beta)$ ⁰-HPFH. Seven heterozygotes with HbS/Black($\text{A}\gamma\delta\beta$)⁰-thalassemia

were identified; these patients were reported to have a mild variant of SCD.[2] Their average HbF was 19.2% but the pattern of HbF distribution was not reported.

Our data are limited by the small sample size and limited follow-up, but it is the largest reported to date of this condition. Due to the rarity of the condition and limited clinical data available, there is no information regarding the type of routine care patients with HbS/Black($\text{A}\gamma\delta\beta$)⁰-thalassemia should receive. In addition to having mild microcytic anemia and hemolysis, patients with HbS/Black($\text{A}\gamma\delta\beta$)⁰-thalassemia are at risk for SCD-related complications, and their clinical course seems to approximate that of individuals with HbS β ⁺ thalassemia, a relatively milder SCD phenotype. This report highlights the importance of definitive diagnosis with DNA-based testing when HbF level is elevated, but laboratory tests do not support the diagnosis of other relatively benign disorders such as HbS/HPFH (e.g. moderate hemolysis, supplemental Table S1).[3]

It is unclear why patients with HbF >20% should have high frequency of SCD-related complications, but symptomatic disease has been described in similar SCD variants with elevated HbF.[4,5] Alleviation of SCD symptoms in patients with the benign variant with HbF>20%, HbS/HPFH, is associated with > 99% distribution of HbF-expressing cells (F-cells).[6] The positive F-cell fraction measured by flow cytometry in two of our symptomatic patients was 92–95%. These results were interpreted as pancellular, although a discrete population of HbF negative cells was detected in both patients (Supplemental Figure S3). Therefore, it is possible that the small percentage of HbF-negative cells in the HbS/Black($\text{A}\gamma\delta\beta$)⁰-thalassemia reflects heterogeneity in HbF expression, which could potentially explain the phenotype differences between HbS/Black($\text{A}\gamma\delta\beta$)⁰-thalassemia and HbS/HPFH populations.

Our data suggest that children with HbS/Black($\text{A}\gamma\delta\beta$)⁰-thalassemia may have SCD-complications and therefore should be monitored by SCD specialists in order to minimize morbidity and potential mortality. Recommendations applicable to patients with SCD, e.g., routine laboratory testing, stroke screening, hydroxyurea therapy, penicillin prophylaxis, and immunizations against encapsulated organisms, should be extended to patients with HbS/Black($\text{A}\gamma\delta\beta$)⁰-thalassemia.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

SCD sickle cell disease

HbS	sickle hemoglobin
HbF	fetal hemoglobin
VOC	vaso-occlusive crisis
OSA	obstructive sleep apnea
MCV	mean corpuscular volume

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Figure 1. Hematologic parameters of patients with Hemoglobin S/Black ($A\gamma\delta\beta$)⁰-thalassemia by age.

Hemoglobin (Hb) remained stable and above 9 g/dL, mean corpuscular volume (MCV) was low or low normal for age, and fetal hemoglobin (HbF) declined but remains above 20% with aging. Age was grouped in 2-year intervals.

Table 1.

Demographics and Laboratory Parameters at Diagnosis and Last Follow-Up.

Patient	Gender	Age(years)	Hb(g/dL)	MCV(fL)	ARC($\times 10^3$ /)	Total bilirubin (mg/dL)	Hb identification(%)	
							HbF	HbS
1	M	0.08	12.1	71	0.055	n/a	88.9	6.3
		13.08	11.3	73.8	0.127	n/a	25.2	n/a
2	M	17.5	13.8	77.2	0.106	1.6	21	75.8
		23.9	12.3	72.5	n/a	n/a	24.7	66.5
3	M	17.5	13.6	78.2	0.091	2	21.4	75.4
		22.9	14.7	74.8	n/a	n/a	21.8	n/a
4	M	0.13	10.6	84.3	0.113	n/a	74.7	13.3
		6.3	11.6	72.9	0.144	n/a	26.3	64.3
5	F	0.5	11.4	72.7	0.109	0.2	34	47.6
		4.0	10.7	66.8	n/a	n/a	26.5	64.8
6	F	1	13.3	71	0.204	0.6	25.9	71.1
		11	12.3	70	0.162	n/a	24.2	74.8
7	M	0.12	10.2	86	0.365	0.4	n/a	n/a
		4.8	11.7	70	0.072	1.6	34	63.5
8	M	0.5	10.8	64	0.146	n/a	32	65.7
		7	8.3	65	0.188	n/a	32.8	64.7
9	M	12	11.9	66	0.084	1.5	24	73
		17	14.2	81	n/a	n/a	n/a	n/a

Notes: M: Male; F: Female; Hb: hemoglobin; MCV: mean corpuscular volume; ARC: absolute reticulocyte count; n/a: not available. Hb identification was performed using high performance liquid chromatography. HbA was zero in all patients.