

Co-Inheritance of Alpha-thalassemia and Sickle Cell Disease in a Cohort of Angolan Pediatric Patients

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INTRODUCTION

Sickle cell disease (SCD) is a recessive hereditary disease and a major global health problem. Even though SCD is a monogenic disease, the clinical manifestations are very heterogeneous due to environmental and genetic factors, in particular, the co-inheritance of alpha-thalassemia and an innate ability to produce fetal hemoglobin, are two major modifiers that have a substantial impact on disease pathophysiology.

Objective: This study aimed to explore the association between alpha-thalassemia, fetal hemoglobin, hematological indices, and clinical serious events in Angolan sickle cell disease pediatric patients. Moreover, we intend to determine the prevalence of 3.7 kb alpha-thalassemia deletion in this population.

- The frequency of 3.7kb alpha-thalassemia deletion was 12.5% for homozygotes and 55% for heterozygote. Additionally, an increase in 3.7 kb alpha-thalassemia deletion frequency was observed in children older than 5 years old (Table 2).
- The presence of the deletion influenced some parameters of the SCD phenotype as shown in Table 3.

Table 2. Frequency of 3.7 kb alpha-thalassemia deletion in total sampled population and subdivided by age group (under 5 and over 5 years old)

3.7 kb alpha-thalassemia deletion genotype	Total sampled population (N=200)	Under 5 years old (N=77; 40%)	Over 5 years old (N=123; 60%)
$\alpha\alpha/\alpha\alpha$	65 (32.50%)	26 (33.80%)	39 (31.70%)
$\alpha\alpha/-\alpha3.7$	110 (55.00%)	42 (54.50%)	68 (55.30%)
$-\alpha3.7/-\alpha3.7$	25 (12.50%)	9 (11.70%)	16 (13.00%)

Table 3. Clinical adverse events and hematological phenotype subdivided by the three alpha-globin genotypes

Data	$\alpha\alpha/\alpha\alpha$		$\alpha\alpha/-\alpha3.7$		$-\alpha3.7/-\alpha3.7$		p
	Mean (SD)	Range	Mean (SD)	Range	Mean (SD)	Range	
Age 1st manifestation months (median)	6	2 - 72	9	2 - 72	11	3 - 96	0.053 ^a
No of transfusions year	0.480 (0.679)	0.00 - 3.75	0.350 (0.409)	0.00-2.43	0.179 (0.170)	0.00-0.50	0.031^b
No of hospitalizations year	0.558 (0.601)	0.00 - 3.14	0.445 (0.447)	0.00-2.50	0.347 (0.327)	0.00-1.20	0.143 ^b
Stroke: yes (N,%)	5 (7.7)	-	1 (0.9)	-	0 (0.0)	-	na
Osteomyelitis: yes (N,%)	5 (7.7)	-	1 (0.9)	-	0 (0.0)	-	na
Splenomegaly: yes (N,%)	6 (9.2)	-	12 (10.9)	-	3 (12.0)	-	0.951 ^c
Splenectomy: yes (N,%)	2 (3.1)	-	1 (0.9)	-	0 (0.0)	-	na
Hepatomegaly: yes (N,%)	12 (18.5)	-	22 (20.0)	-	1 (4.0)	-	0.158 ^c
Hemoglobin (g/dL)	7.246 (0.987)	5.10 - 9.30	7.236 (0.981)	4.70-10.50	7.788 (1.237)	5.10-10.50	0.044^b
MCV (fL)	81.755 (5.387)	69.90-93.20	76.216 (6.745)	57.60-107.10	62.736 (5.761)	55.60-81.50	0.000^b
MCH (pg)	27.289 (2.054)	21.60-31.20	25.055 (2.248)	19.30-30.40	20.252 (1.957)	18.40-28.60	0.000^b
WBC (10 ⁹ /L)	15.574 (4.705)	7.86-35.47	14.628(4.886)	6.15-35.11	13.219 (7.519)	4.39-44.79	0.150 ^b
Neutrophils count (10 ⁹ /L)	6.715(2.910)	2.49-15.97	6.680 (3.640)	1.06-25.52	6.321 (3.032)	1.98-12.43	0.887 ^b
Platelet count (10 ⁹ /L)	441.369 (164.644)	162.00-1004.00	427.200 (209.119)	68.00-1710.00	42.600 (188.165)	114.00-922.00	0.087 ^b
Reticulocyte count (10 ⁹ /L)	11.623 (4.513)	3.92-26.68	10.669 (5.364)	2.94-39.37	6.462 (4.457)	0.67-17.08	0.000^b
Fetal Hemoglobin (%)	6.347 (4.539)	0.80-23.60	5.634 (4.000)	0.00-23.80	4.917 (3.468)	1.20-12.50	0.304 ^b

Bold indicates the significant values (p < 0.05) na test not performed due to empty cells, SD standard deviation

^a Kruskal-Wallis non parametric test ^b ANOVA

METHODS

SCD patients	<ul style="list-style-type: none"> Age: 3 to 12 years None of them was treated with hydroxyurea or transfusion in the last 3 months
Clinical characterization	<ul style="list-style-type: none"> Demographic data Clinical history Physical examination
Laboratory characterization	<ul style="list-style-type: none"> Complete blood count Reticulocyte count Quantification of fetal hemoglobin
Molecular study	<ul style="list-style-type: none"> 3.7 kb alpha-thalassemia deletion was studied by GAP-PCR
Data analysis	<ul style="list-style-type: none"> ANOVA Kruskal-Wallis non-parametric tests Pearson χ^2 tests

RESULTS

Table 1. Demographic and clinic characteristics

Variable	Values
A total SCD children	200
Age (years)	6.6 (3-12)
Gender:	
- females	103 (51.5%)
- males	97 (48.5%)
Age 1st manifestation months (median)	13.6 (2-96)
Stroke (n., % of patients)	6 (3%)
Osteomyelitis (n., % of patients)	6 (3%)
Hospitalizations (n., % of patients)	166 (83%)
Transfusions (n., % of patients)	135 (67.9%)
Hemoglobin (g/dL)	7.3 (4.7 - 10.5)
VGM (fL)	76.3 (55.6 - 107.1)
HGM (pg)	25.1 (18.0 - 31.0)
Reticulocytis count (%)	10.4 (0.67 - 39.37)
Fetal hemoglobin (%)	5.72 (0.0 - 23.8)

CONCLUSION

- The prevalence of 3.7 kb alpha-thalassemia deletion in Angolan sickle cell pediatric patients was 12.5% of homozygotes and 55% of heterozygotes.
- The number of deletions was associated with less severe phenotypes in these sickle cell Angolans patients.
- There were no significant differences in fetal hemoglobin between the three groups of genotypes. Although it was not significant, we observed lower fetal hemoglobin values in 3.7 kb alpha-thalassemia deletion homozygotes.
- Improved hematological indices, lower blood transfusions, hospitalizations rate and stroke events, contributing to an improvement of the general well-being and probably improving the survival of SCD homozygous for alpha-thalassemia

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