Blood pressure in children with sickle cell disease

Pressão arterial em crianças portadoras de doença falciforme

Presión arterial en niños portadores de enfermedad falciforme

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ABSTRACT

Objective: To evaluate blood pressure (BP) in children with sickle cell disease (SCD).

Methods: Observational descriptive study of BP in 70 children with SCD. BP values were classified according to the V Brazilian Guidelines in Arterial Hypertension. Patients were divided into groups according to genotype (HbSS, HbSC) and according to age: group I, three to four years and 11 months; group II, five to eight years and 11 months; and group III, nine to 13 years and 11 months. The Student's *t* test and ANOVA were used for statistical analyses, and the level of significance was set at $p<0.05$.

Results: Mean and standard deviation (SD) of systolic BP (SBP) (mmHg) were 95.9±11.45, and of diastolic BP (DBP), 62.6±7.78. Means according to age group were: group I - SBP 91.2±5.78 and DBP 61.5±7.15; group II - SBP 97.3±10.86 and DBP 64.4±7.89; and group III - SBP 100.0±9.88 and DBP 61.5±4.94. Results showed that 5.7% of the patients had hypertension and 8.6%, pre-hypertension. Mean SBP and DBP of HbSC and HbSS patients did not differ.

Conclusions: Further studies should be conducted to assess BP in patients with SCD and determine possible causes of hypertension in these patients.

Key-words: blood pressure; hypertension; anemia, sickle cell; child.

RESUMO

Objetivo: Avaliar os valores da pressão arterial (PA) em crianças portadoras de doença falciforme (DF).

Métodos: Estudo observacional unicêntrico descritivo de 70 crianças portadoras de DF. Os valores da PA obtidos foram classificados conforme as V Diretrizes Brasileiras de Hipertensão Arterial. Os pacientes foram distribuídos segundo o genótipo em grupo HbSS e HbSC e segundo a faixa etária: grupo I (três anos a quatro anos e 11 meses), grupo II (cinco anos a oito anos e 11 meses) e grupo III (nove anos a 13 anos e 11 meses). Na análise estatística, aplicou-se o teste *t* de Student e a ANOVA, sendo significante $p<0,05$.

Resultados: A média e o desvio padrão (DP) das medidas da PA sistólica (PAS) (mmHg) foram 95,9±11,45 e da PA diastólica (PAD) 62,6±7,78. As médias da PA por faixa etária foram: grupo I, PAS 91,2±5,78 e PAD 61,5±7,15; grupo II, PAS 97,3±10,86 e PAD 64,4±7,89; e grupo III, PAS 100,0±9,88 e PAD 61,5±4,94. Observou-se que 5,7% dos pacientes apresentavam hipertensão arterial (HA) e 8,6% eram pré-hipertensos. A média dos valores da PAS e PAD entre os pacientes HbSS e HbSC não diferiu.

Conclusões: Novos estudos devem ser realizados para avaliar PA em pacientes com DF e detectar as possíveis causas de HA nesses pacientes.

Palavras-chave: pressão arterial; hipertensão; anemia falciforme; criança.

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RESUMEN

Objetivo: Evaluar los valores de la presión arterial (PA) en niños portadores de enfermedad falciforme (EF).

Métodos: Estudio observacional unicéntrico descriptivo de PA de 70 niños portadores de EF acompañadas en el ambulatorio de Hematología Pediátrica. Los valores de la PA obtenidos fueron clasificados conforme a las V Directrices Brasileñas de Hipertensión Arterial. Los pacientes fueron distribuidos según el genotipo en grupo HbSS y HbSC, y según la franja de edad: grupo I (tres años a cuatro años y 11 meses), grupo II (cinco años a ocho años y 11 meses) y grupo III (nueve años a 13 años y 11 meses).

Resultados: El promedio y la desviación estándar (DE) de las medidas de la PA sistólica (PAS) (mmHg) fueron 95,9±11,45 y de la PA diastólica (PAD) 62,6±7,78. Los promedios de la PA por franja de edad fueron: grupo I, PAS 91,2±5,78 y PAD 61,5±7,15; grupo II, PAS 97,3±10,86 y PAD 64,4±7,89; y grupo III, PAS 100,0±9,88 y PAD 61,5±4,94. Se observó que el 5,7% de los pacientes presentaban hipertensión arterial (HA) y el 8,6% eran pre-hipertensos. El promedio de los valores de la PAS y PAD entre los pacientes HbSS y HbSC no difirió significativamente. En el análisis estadístico, se aplicó la prueba *t* de Student y ANOVA, siendo significante $p<0,05$.

Conclusiones: La detección de HA en niños confirma la importancia de verificar la PA en la rutina pediátrica. Nuevos estudios deben realizarse para evaluar la PA en pacientes con EF y detectar las posibles causas de HA en esos pacientes.

Palabras clave: presión arterial; hipertensión; anemia falciforme; niño.

Introduction

Sickle cell disease (SCD), the most frequent hematological disease in Brazil, affects an important portion of the population in different countries. Brazilian authors estimate 3,500 new cases per year[1,2]. The HbS gene may combine with other hereditary hemoglobin anomalies, such as hemoglobin C, hemoglobin D and β-thalassemia, and generate combinations that are also symptomatic, called hemoglobinopathy SC, hemoglobinopathy SD and S/β-thalassemia. All these symptomatic forms of expression of the HbS gene are known as SCD.

The epidemiological features, clinical signs and symptoms and hematological characteristics of SCD vary according to genotype, and the HbSS genotype is the most severe form of the disease. It leads to numerous complications, such as acute vaso-occlusive events and chronic disease, which may affect almost all organs and systems and result in high morbidity and a shorter life expectancy among these patients[2].

Kidney problems, common in SCD, start in childhood. About one third of all adolescents and young adults with SCD have nephropathies and renal abnormalities, such as impaired urinary concentration ability, defects in urinary acidification and potassium excretion, as well as glomerular disorders, such as glomerular hyperfiltration and proteinuria[3-5] Hypertension (HT), although frequent in African ethnicities, has not been frequently diagnosed in patients with SCD[3]. Studies with adults with SCD showed that they had a lower incidence of HT and lower blood pressure (BP) values than patients without hemoglobinopathy S, but these findings have not been confirmed in pediatric populations[6-10]. Gordeuk *et al*[11] found that patients with SCD have a higher risk of pulmonary hypertension and renal failure when their blood pressure was elevated.

The evaluation of BP in children and adolescents should be part of the clinical pediatric routine, and normative values for healthy children and adolescents are already available[12]. However, few studies have evaluated BP in children with SCD. This study evaluated BP in children and adolescents with SCD followed up in the Pediatric Hematology Department of Escola Paulista de Medicina, Universidade Federal de São Paulo (EPM-Unifesp), São Paulo, Brazil, to investigate whether BP values are similar to those found among children without hemoglobinopathies and whether HT, a risk factor for stroke and pulmonary hypertension among patients with SCD, is also found in this population. Results were compared with BP values used in the literature for pediatric populations and evaluated according to the nutritional status of the patients included in this study.

Method

This observational descriptive study was conducted in the Outpatient Pediatric Hematology Service of EPM-Unifesp, São Paulo, Brazil, from March 2006 to July 2007. This study enrolled all patients with SCD (hemoglobinopathy HbSS and HbSC) aged three to 14 years, who were seen in the outpatient service during the study. The patients were distributed into groups according to genotype (HbSS and HbSC) and according to age: group I – three to four years and 11 months; group II – five to eight years and 11 months; and group III – nine years and 13 years and 11 months.

Patients were excluded if they had hemoglobinopathy HbS β-thalassemia, were receiving treatment with corticosteroids, anti-inflammatory, anticonvulsant or antihistaminic drugs, bronchodilators, digitalis or BP lowering agents or, at the time of data collection, had a fever or a sickling crisis.

This study was approved by the Ethics in Research Committee of Unifesp under no. 0437/03. Parents or guardians received information about the study and provided written consent for participation.

BP, weight and height were measured by the same author (pediatric nephrologist) in the morning, and a specific form was used to record data. Three BP measurements were made for each patient at three different times, always by the same author, and all care was taken to minimize anxiety and fear of the procedures. Measurements were made using an aneroid sphygmomanometer (Lane, Medsafe Ltd., Cambridge, United Kingdom), acquired from OPAS and regularly calibrated, and the cuffs were size six, eight, 10 or 12 (Welch Allyn, Welch Allyn Inc, Skaneateles Falls, NY). BP measurements followed the V Brazilian Guidelines in Arterial Hypertension[12]. BP values for the groups of patients were compared with BP values established in the literature and defined in the V Brazilian Guidelines in Arterial Hypertension[12]. Systolic (SBP) and diastolic BP (SBP and DBP) were defined as normal when below the value of the 90th percentile for age, sex and height percentile, as long as below 120/80mmHg. The borderline value was defined as BP equal to or greater than the 90th percentile and below the 95th percentile for age, sex and height percentile; for adolescents, any value equal to or greater than 120/80mmHg was classified as borderline, even if below the 95th percentile for age, sex and height percentile. HT was defined as BP equal to or greater than the 95th percentile for age, sex and height percentile[12].

A digital platform scale (Filizola®, Filizola S.A., São Paulo, Brazil) was used to measure weight, and a wooden vertical stadiometer was used for height; the horizontal rod was adjusted to rest on the top of the head at a right angle with the vertical ruler. Anthropometric measurements were made with the patient barefooted and wearing as little clothing as possible. Anthropometric data and the nutritional status were analyzed using the Epi-Info 6.04b software, Microsoft® Excel, and the WHO Anthro 2006[13] and Anthro Plus 2007[14]. The anthropometric indices used to evaluate nutritional status were weight/age (W/A), height/age (H/A) and weight/height (W/H) expressed as Z scores. Nutritional status according to BMI was classified using the growth charts issued by the World Health Organization (WHO).

Quantitative variables were described as central tendency measures and compared using the Student's *t* test. ANOVA was used to compare the variables between the different age groups. The level of significance was set at 5% ($p<0.05$) for all tests.

Results

This study included 70 patients (35 girls, 50%) aged three years and two months to 14 years (mean[SD] = 7.2±3.2; median = 6.1 years). Genotype was HbSS for 44 (63%) patients and HbSC for 26 (37%).

Mean (mmHg) values and standard deviations for SBP and DBP were 95.9±11.4 and 62.6±7.7. In the groups of patients with genotypes HbSS and HbSC, SBP was 97.7±10.1 and

Table 1 - Anthropometric data of patients with sickle cell disease according to age group

	Group I (n=24)	Group II (n=27)	Group III (n=19)	*p*-value
Height (cm)				
mean	103.6±5.5	120.4±8.5	138.8±7.7	<0.001
Percentile	60.0±24.6	36.1±27.2	20.8±22.5	<0.001
H/A Z score	0.24±1.29	-0.22±0.74	-1.41±1.05	<0.001
Weight (kg)				
mean	16.4±2.3	22.8±3.9	30.8±7.0	<0.001
Percentile	52.7±29.0	45.1±22.9	13.2±18.4	<0.001
W/A Z score	0.04±0.92	-0.12±0.70	-1.68±1.29	<0.001
W/H Z score	-0.31±0.96	0.11±0.47	–	<0.001
BMI				
mean	15.5±1.3	15.7±1.3	15.8±11.9	0.227
BMI Z score	-0.42±1.29	-0.01±0.74	-1.09±1.04	0.012

H/A: height/age; W/A: weight/age; BMI: body mass index

Table 2 - Systolic blood pressure and diastolic blood pressure of patients with sickle cell disease according to age group

Parameter	Group I (n=24)	Group II (n=27)	Group III (n=19)	*p*-value
SBP (mmHg)				
Mean±SD	91.2±5.8	97.3±10.9	100.0±9.9	0.006
Median	90	98	100	
Q1	88	90	90	
Q3	94	104	108	
DBP (mmHg)				
Mean±SD	61.5±7.1	64.4±7.9	61.5±4.9	0.229
Median	60	63	60	
Q1	56	60	58	
Q3	66	70	64	

SBP: systolic blood pressure; DBP: diastolic blood pressure; SD: standard deviation; Q1: 1st quartile; Q3: 3rd quartile

Table 3 - Mean systolic blood pressure of patients with sickle cell disease according to nutritional status and age group

	Normal weight	n	Risk of PEM	n	*p*-value
Group 1	91.1±5.8	20	90.4±3.2	04	0.283
Group II	97.3±10.8	22	-	02	NA
Group III	99.3±10.0	09	100.1±7.8	10	0.386

NA: not analyzed; PEM: protein-energy malnutrition

Table 4 - Mean diastolic blood pressure of patients with sickle cell disease according to nutritional status and age group

	Normal weight	n	PEM risk	n	*p*-value
Group 1	61.2±7.3	20	60.4±5.4	04	0.345
Group II	64.4±7.8	22	-	02	NA
Group III	61.5±5.1	09	63.7±4.4	10	0.463

NA: not analyzed; PEM: protein-energy malnutrition

93.0±8.4 (p=0.060) and DBP was 62.4±7.1 and 62.53±8.7 (p=0.460).

The anthropometric and nutritional status deteriorated significantly with age (Table 1). Protein-energy malnutrition (PEM) was found in five patients (7.14%), two in group I and three in group III. The risk of PEM was found in 12 (17,1%) patients, five in group I and seven in group III.

SBP, but not DBP, became significantly higher with age (Table 2).

HT was confirmed in four (5.71%) of the patients, two in group I (one HbSC and one HbSS) and two in group II (both HbSS), but there were no differences between sexes. Borderline BP was found in six (8.6%) patients, one (HbSC) in group I and five in group II (four HbSS and one HbSC); all five patients were boys. The anthropometric profile of the four patients with HT and the six with borderline BP did not differ significantly from the profile of the other patients.

SBP and DBP in the group of patients with malnutrition and risk of malnutrition were not significantly different from BP values in the group of patients with normal weight (Tables 3 and 4).

Discussion

BP increases progressively with age: SBP is below 100mmHg in children younger than six years and reaches 120/80mmHg in adulthood. Considered optimal[12], such variation may be understood as a physiological adaptation to physical development. In children, BP changes progressively with age, and studies demonstrated that, for that to occur, there must also be an increase in weight and height[15,16].

Anthropometric results in this study are similar to those found in the literature and describe that patients with SCD may have, starting at two years of age, a body

growth delay that affects weight more than height and accentuates progressively up to 18 years of age[17]. Mean SBP and DBP in our study are similar to those found in studies with healthy children conducted by Brandão[18], Moura *et al*[19], and Sarni *et al*[20].

Martorell *et al*[21] evaluated BP in children without any hemoglobinopathies and reported that those with PEM had BP lower than normal-weight children, but our study did not confirm it. The number of patients with PEM in our sample was small, which reduces analytical power. Several studies[6-10] with adults found that SCD is associated with lower BP values and lower incidence of HT than among the general population, which may be a beneficial factor, because HT is a risk factor for sickling crises, pulmonary hypertension and strokes[11].

This study found that BP was abnormal (hypertension and pre-hypertension) in 14.3% of the patients, in agreement with findings reported by Becton *et al*[5] in a study with 90 patients with SCD and ages ranging from two to 18 years. The detection of 5.7% of the patients with HT is also similar to findings reported in studies conducted with adults and children with SCD, as well as the values found in the Brazilian and international literature for healthy children and adolescents[4,17,19,22]. In the study conducted by 10 patients (11.1%) had hypertension, and four of them also had microalbuminuria.

The identification of patients with pre-hypertension should be seen as a warning sign because there is greater risk of progressing into HT[23], which occurred in 8.6% of the cases in the sample under evaluation in our study. Becton *et al*[5] also found a similar percentage (6.2%), and one of their patients had microalbuminuria.

Studies with children have found an association between HT and BMI[23-25]. We did not confirm such association, probably because BMI was normal and unaltered in all groups. However, other factors may explain those findings: patients with SCD have changes in plasma renin, endothelin and nitric oxide metabolites because of vaso-occlusion, and those changes affect the balance between vasodilatation and vasoconstriction, which is not seen in undernourished children[26-28].

Findings of HT in children with SCD stress the importance of measuring BP. Patients with BP above mean values are also exposed to greater risks of vaso-occlusive crises and death.

Mean SBP and DBP in our study were similar to those found in studies with healthy children without any hemoglobinopathies. The identification of abnormal BP (hypertension and pre-hypertension) in patients with SCD confirms the importance of routine BP measurements in pediatric routine. Multi-center studies should be conducted to evaluate BP in children and adolescents with SCD and detect possible causes of hypertension among these patients.

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