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Blood Pressure of Children and Adolescents with Sickle Cell Anemia in Basra, Iraq

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ABSTRACT

Background: Blood pressure in patients with sickle cell anemia (SCA) is influenced by autonomic cardiovascular dysfunction, endocrinopathies, nephropathy and nutritional factors. We aimed to evaluate systemic and diastolic blood pressure and its severity among children and adolescents with SCA and determine its association with clinical and hematological variables.
Methods: This case-control study included 112 patients with SCA (6-17 years old), registered at Basra Center for Hereditary Blood Diseases and 133 age and sex-matched healthy subjects as a control group. Complete examination was done for all subjects including anthropometric and BP measurements. Complete blood count, blood urea and serum creatinine were measured for all participants. A multivariate correlation analysis was used to assess contributing factors in BP.
Results: The systolic BP (SBP) and diastolic BP (DBP) curves of patients with SCA showed lower levels than control group for all age groups. Although both SBP and DBP readings were comparable at late adolescence. Pre-hypertension was reported in 5 (4.4%) patients and 3 (2.4%) healthy subjects. Multivariate analysis revealed that SBP and DBP among patients with SCA had significant positive association with age, weight, height, body mass index, hemoglobin and blood transfusion history and a negative association with heart rate ($P<0.05$).
Conclusion: Our findings supported previous reports of lower BP in patients with SCA. Furthermore, routine BP measurements in pediatric patients with SCA is important for early detection of pre-hypertension to establish an effective treatment.

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Introduction

The gene for sickle cell anemia (SCA) is widespread throughout the world being more prevalent in Africa, Mediterranean countries, Middle East and parts of India.[1] In Iraq, the frequency of sickle- cell gene in Basra is 6.5%, which is much higher than the reported prevalence of 1.2% in Duhok in north of Iraq.[2,3]

The pathophysiology of SCA is complex that involves hemoglobin polymerization, leading to erythrocyte rigidity and vaso-occlusion, chronic anemia, hemolysis, and vasculopathy. Recurrent episodes of vasoocclusion and inflammation result in progressive damage to most organs including the brain, kidneys, lungs, bones, and cardiovascular system which becomes apparent with increasing age.[4] All these factors play an important role in regulation of blood pressure (BP) in patients with SCA through many hormonal and autonomic factors.

Many studies reported low systemic BP in children with SCA.[5-7] Proposed mechanisms include sodium and water wasting as a result of renal medullary defect,[5,8] systemic vasodilation mediated by cardiovascular autonomic dysfunction,[9] impaired response to major endothelial vasodilators such as nitric oxide (NO), reduced vascular reactivity,[10,11] and zinc deficiency

which is another contributing factor to BP changes in SCA. Many enzymes involved in the regulation of BP, like nitric oxide synthase, angiotensin-converting enzyme and neutral endopeptidases contain zinc in their structure.[12-14]

Frequent transfusions lead to iron accumulation and overload; which circulates as non-transferrin bound iron (NTBI), that subsequently form reactive oxygen species (ROS) that lead to endothelium and end organ damage like thyroid and adrenal glands. BP regulation is also supported by circulating hormones from these glands.[7,15]

Numerous studies have reported high systemic BP results in patients with SCA due to pulmonary hypertension (PHT) and renal dysfunction.[16-18] The high systolic BP increases the risk of stroke in patients with sickle cell disease (SCD).[6,19] Some other studies have not revealed a significant difference for BP between patients and control group.[20,21]

The current study was aimed to assess the systemic BP and its possible severity in patients with SCA in comparison with sex and age matched healthy children and adolescents.

Materials and Methods

Study Population

A case-control study has been carried out on children and adolescents with SCA referring to "Center for Hereditary Blood Diseases" since March-November 2013. A total of 112 patients (61 males and 51 females) with homozygous hemoglobin S (Hb SS) on High performance Liquid Chromatography, from 6-17 years were evaluated while in a steady state period. Steady state was defined as absence of any painful crisis in the preceding 4 weeks and absence of any symptom or sign attributable to acute illness.[22,23]

Detailed clinical data regarding the disease and any history of SCA-related complications were obtained from patients or caregivers in addition to reviewing the patient's medical records.

Severity of SCA was assessed according to the frequency of vaso occlusive crises (VOC) requiring hospitalization, history of blood transfusions, history of acute chest syndrome (ACS), avascular necrosis of bones (AVN) or stroke. Severe disease was defined as frequent VOC requiring hospitalization ≥3 /year, blood transfusion ≥3 /year, frequent hospitalization ≥3 /year, an episode of ACS, AVN or stroke.[24,25]

Drugs taken by patients such as non-steroidal anti-inflammatory drugs (NSAIDs), digoxin for heart failure and iron chelating agents were also recorded. Growth parameters and vital signs were measured and physical examination was performed in all patients.

The control group included 133 age and sex-matched apparently healthy children and adolescents, aged 6-17 years, who were attending 3 primary schools and two secondary schools. Information obtained included past medical history, use of medications and family history of hypertension. Physical examination was carried out including vital signs and growth measures.

Children and adolescents were excluded in the presence of any congenital or acquired heart and renal disease, intercurrent illnesses like fever and infection and medications such as digoxin and antihypertensive drugs.[22,23] Patients on hydroxyurea (HU) were also excluded as HU can limit some of the early symptoms and signs of renal involvement and modify disease severity.[26]

Anthropometry

All patients enrolled in the study were weighed, wearing light clothing. Height was taken barefooted to the nearest 0.1cm. Both weight and height were measured using Electronic body Tes-200 RC scale. Height and weight for control group was measured using minimeter portable device and electronic body scale, respectively.

Body mass index (BMI) was calculated for all subjects based on the formula: BMI: Weight in kilogram /(Height in meter)^2.

Blood Pressure Measurements

Standard methodology as recommended by the Fourth report on diagnosis, evaluation and treatment of high blood pressure in children and adolescents was used to measure blood pressure.[27] The brachial blood pressure was measured in calm of children after 5-10 min resting in the seated position with the arm on the same level as the heart with mercury sphygmomanometer of appropriate cuff size. BP measurements for three times was performed for each participant; all were carried out by the same investigator.

Hypertension (HTN) was defined as average systolic blood pressure (SBP) and/or diastolic blood pressure (DBP) equal or greater than 95th percentile for age, sex and height. Pre-hypertension in children was defined as average SBP or DBP ≥90th percentile, but less than 95th percentile,[27] while low BP was defined as a blood pressure value <5th percentile or below 2 standard deviation of the mean for age and sex.[28]

Informed consent was obtained from all subjects and their families before enrollment in the study.

The study was approved by the Ethical Committee of Basra Medical College as part of a thesis submitted to the Iraqi Scientific Council of Pediatrics Specialization.

Laboratory Data

Patients were diagnosed to be homozygous Hb SS using High Performance Liquid Chromatography (HPLC), (VARIANT™, β-Short Programs; Bio-Rad Laboratories, Hercules, CA, USA).

CBC was performed using SYSMEX KX-21N Automated Hematology Analyzer Minidary BC5300 (in patient group). For the control group hemoglobin level was estimated using portable device (Mission Hemoglobin Testing System c111-3011).

Blood urea and serum creatinine were estimated by spectrophotometer (EMCLAB) using wave length of 578 nm and 520 nm respectively. These tests were done for patients only.

Statistical Analysis

All statistical analyses were carried out using the Statistical Packages for Social Sciences (SPSS Inc.,

Chicago, IL, USA) software version 17.0. Data were expressed by mean±standard deviation. Comparisons of proportions were performed by cross tab using Chi-Square test. Intra-class difference in parameters between two means of different samples was analyzed using independent t-test. Inter-class difference in blood pressure in the patients was compared by one-way Analysis of Variance (ANOVA) and Post Hoc multiple comparison of means by using Scheffe test. Statistical tests with P-values <0.05 were considered statistically significant. A multivariate correlation analysis was measured to assess the potential risk factors associated with SBP and DBP.

Results

245 patients; 112 patients with SCA and 133 healthy children and adolescents enrolled in this study. The mean age (±SD) of patients with SCA was 10.69±3.43 years and for control group was 10.73±3.13 years. Patients with SCA had a significantly lower growth parameters including weight, height and BMI than control group (P<0.05). In addition, SBP and DBP were significantly lower while heart rate was significantly higher among patients with SCA compared to control group (P<0.05) (Table 1).

Among patients with SCA; 87 (77.7%) and 107 (95.6%) had normal SBP and DBP, respectively compared to 130 (97.6%) with normal SBP and DBP in the control group. Pre-hypertension was reported in 5 (4.4%) of patients and 3 (2.4%) of healthy subjects, while 20 (17.9%) of patients had low SBP and none of control group had low SBP or DBP. High SBP and DBP were not reported in all studied subjects.

The SBP and DBP curves of patients with SCA showed a level lower than the control group among all age groups. Although SBP and DBP readings were comparable among late adolescents (Figures 1 and 2).

There was no significant difference in SBP and DBP between men and women with SCA (92.13±14.84 and 94.34±13.52) and (61.14±10.62 and 61.86±8.88), respectively. [(P=0.422) and (P=0.703), respectively].

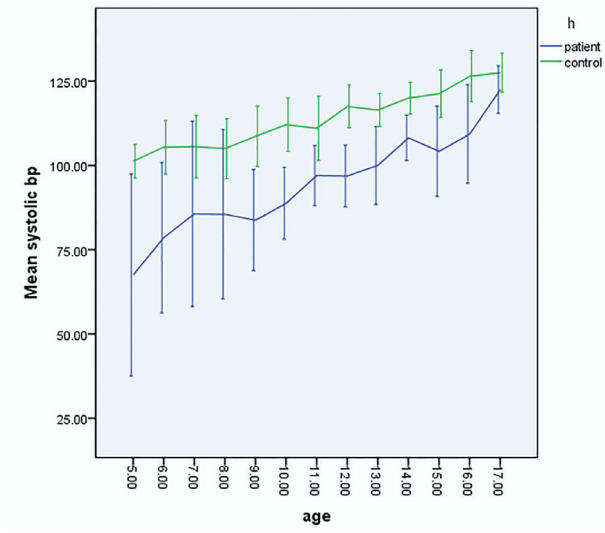

Figure 1: Mean systolic blood pressure for patients with SCA and control group in relation to age.

Out of the 112 studied patients; 68.7% had a history of VOC, 62.5% had a history of blood transfusion, 58% of them had been hospitalized in the last year and 19.6% had history of ACS. Only one patient had a history of stroke while there was not any patient with AVN of bones in this study. Patients with frequent transfusions ≥3 /year had higher SBP and DBP, while those with VOC ≥3 /year had a significantly lower DBP (P<0.05) (Table 2).

Assessing comparison of the mean of BP using Scheffe test revealed that the observed difference in SBP was explicated by the difference between those who had not been transfused and those with ≥3 transfusions (P=0.028). While the observed difference in DBP was explained by the difference between patients with no VOC and those with more than 3 VOC (P=0.041), patients without hospitalization and those with more than 3 hospitalizations (P=0.047) and those without history of

Table 1: Selected demographic and clinical variables of children and adolescents with SCA and control group

Variable		SCA group (No 112)	Control group (N0 133)	P value
Age (years)				
Mean±SD		10.69±3.43	10.73±3.13	0.600*
Age		No (%)	No (%)	
Age Groups (Years)	6-9	36 (32.14)	35 (26.32)	0.092**
	10-13	40 (35.72)	61 (45.86)	
	14-17	36 (32.14)	37(27.82)	
Gender		No (%)	No (%)	
Female		51(45.54)	64 (48.12)	0.686**
Male		61(54.56)	69 (51.88)	
Selected clinical variables (mean±SD)				
Weight (kg)		27.87±10.72	33.18±10.78	<0.001*
Height (cm)		130.67±22.71	138.33±16.49	<0.001*
BMI (kg/m^2)		15.44±2.50	16.78±1.97	<0.001*
SBP (mmHg)		93.12±14.23	113.01±7.75	<0.001*
DBP (mmHg)		61.47±9.83	68.87±6.14	<0.001*
Heart rate		106.34±6.35	83.35±8.78	<0.001*

BMI: Body mass index; SBP: Systolic blood pressure; DBP: Diastolic blood pressure. *Independent t- test was used to measure P value, **chi-square was used to measure P value

transfusion versus the group with transfusion (P=0.025).

Among patients with SCA, those with Pre-HTN state had a significantly higher Hb, serum creatinine and blood urea levels than those with low and normal BP (P<0.05). Multiple comparisons of mean Hb using Scheffe test showed that the observed difference in Hb was accounted for by the difference between the low BP and Pre-HTN groups (P=0.021) and normal BP and Pre-HTN groups (P<0.001). For blood urea the observed difference was accounted for by the difference between the low BP and Pre-HTN groups (P=0.038) and normal BP and Pre-HTN groups (P<0.001), and for serum creatinine was explained by the difference between the low BP and Pre-HTN groups (P=0.032) and normal BP and Pre-HTN groups (P<0.001) (Table 3).

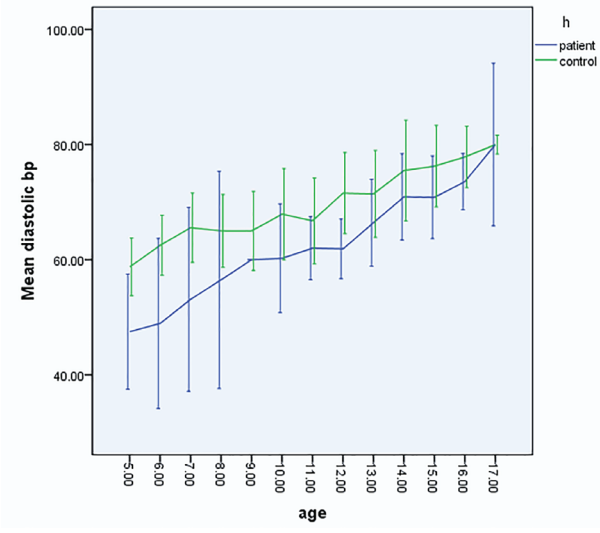

Figure 2: Mean diastolic blood pressure for patients with SCA and control group in relation to age.

Multivariate analyses of different factors that could be associated with BP in patients with SCA showed that both SBP and DBP have a positive association with age, weight, height, BMI, Hb and transfusion history and a negative association with heart rate (Table 4).

Discussion

The current study assessed systemic BP of children with SCA in Basra, southern of Iraq; where the frequency of the disease is the highest in comparison with other regions of Iraq.

Our study revealed a lower SBP and DBP among patients with SCA compared to age and gender-matched healthy children and adolescents, although both SBP and DBP

Table 2: Blood pressure among patients with SCA in relation to disease severity

Variables		SBP Mean±SD	P value	DBP Mean±SD	P value
Transfusion /year	None (42)	72±11.41	<0.001	52 ±7.85	<0.001*
	<3 (36)	97±10.40		63 ±8.14	
	≥3 (34)	100±11.16		65±10.48	
VOC /year	None (35)	98±17.45	0.156	64±8.43	0.026*
	<3 (55)	95±15.44		62±10.88	
	≥3 (22)	91±13.54		60 ±10.08	
Hospitalization /year	None (47)	93±13.36	0.058	60±9.47	0.128*
	<3 (56)	94±16.15		62±10.08	
	≥3 (9)	98±16.39		68±11.18	
ACS	No (90)	95±14.06	0.395	62±9.79	0.328**
	Yes (22)	88±17.19		61±11.18	

VOC: Vaso occlusive crisis; ACS: Acute chest syndrome. *ANOVA was used, **Independent t-test was used

Table 3: Selected hematological and renal variables in relation to blood pressure

Variables		Low BP	Normal BP	Pre-HTN	P value
Hb (g/dl)		7.67±1.06	8.27±1.31	10.46±0.20	<0.001
WBC (10^9/l)	Total WBC	12.75±1.51	11.69±8.31	8.40±3.71	0.671
	Neutrophils	5.10±0.46	5.30±0.54	5.25±0.50	0.650
B. urea (mmol/l)		4.44±1.06	4.92±1.02	10.50±0.35	<0.001
S. Cr (mmol/l)		71.90±6.91	73.05±10.26	91±2.12	<0.001

Values were expressed as mean±SD, ANOVA test was used to measure P value for all variables

Table 4: Association of systolic and diastolic blood pressure with related variables

Parameter	Systolic BP	P value	Diastolic BP	P value
	*r		*r	
Age	0.591	<0.001	0.726	<0.001
Weight	0.703	<0.001	0.664	<0.001
Height	0.632	<0.001	0.686	<0.001
BMI	0.491	<0.001	0.466	<0.001
Hb	0.587	<0.001	0.340	<0.001
VOC	-0.184	0.053	-0.156	0.101
Transfusion History	0.0587	0.02	0.403	<0.001
Heart rate	-0.593	<0.001	-0.439	<0.001

BMI: Body mass index; VOC: Vaso occlusive crises; *r: Correlation coefficient

readings were comparable during late adolescents. In addition, the BP among patients with SCA was significantly associated with age, nutritional status and selected markers of disease severity (Hb and transfusion history).

Blood pressure in patients with SCA is influenced by many factors including autonomic cardiovascular dysfunction, multiple endocrinopathies, nephropathy and nutritional factors secondary to chronic anemia and iron overload.[8,9,15]

The lower SBP and DBP is possibly related to the progressive renal tubular defect which begins at about 7 years of age and the increased sodium and water loss, lower BMI, alteration in peripheral vascular resistance and vasodilation.[5,6,29]

Many studies on children and adolescents with SCA have shown conflicting results; similar findings of lower BP among patients were reported by Animasahun et al.[5] in Nigeria, Pegelow et al.[6] in USA, and Homi et al.[7] in Jamaica. However, Shatat et al.[30] in Charleston and Becker et al.[18] have reported high SBP and DBP among adolescent patients with SCA. Ekure et al in Nigeria did not report a significant difference in SBP and DBP between children with SCD and control group.[20]

The comparable SBP and DBP of patients with that of control group in late adolescence is possibly explained by the increase in weight and adipose tissue with increasing age and their influence on BP in children and adolescents appears to be through increased sympathetic activity and renin- angiotensin-aldosterone system activation which result in increased SBP and DBP, in addition to deterioration in renal function.[16,31] Homi et al.,[7] and Pegelow et al.[6] reported similar results likewise.

This study also identified other factors that might be determinants of BP in SCA. These include age, weight, height, BMI, and frequency of VOC and blood transfusion. We noted significant positive association between SBP and DBP with age, weight, height, BMI, Hb and transfusion and a negative association with pulse rate. Furthermore, DBP also showed a negative association with VOC.

These findings were consistent with that of Oguanobi et al.[23] in Nigeria, and Pegelow et al.[6] who reported that BMI correlates positively with SBP and DBP. Homi et al reported that low weight is a risk factor for low SBP and DBP. The effect of low weight is mainly due to plasma renin activity and aldosterone level as both decrease with underweight and result in decreasing the systemic BP.[7] In addition, poor growth is usually associated with low hemoglobin level which causes low blood pressure through the underlying physiology related to anemia-associated systemic vasodilatation and decreased systemic vascular resistance.[32,33]

A positive association between SBP and DBP and hemoglobin level was found in our patients which was consistent with other studies.[7,23,34,35]

Wolf et al reported that higher hemoglobin measurements at baseline were associated with greater height (P<0.001), weight (P=0.000), SBP (P<0.001), and DBP (P=0.003) measurements.[36] This is possibly explained by the circulatory response to anemia with resultant reduced peripheral vascular resistance resulting in fall in blood pressure in patients with severe anemia.[21]

Evidence suggests that children receiving regular blood transfusion as an alternative therapeutic strategy for increasing Hb level had significantly increased height and weight growth velocity compared to children with SCA not receiving transfusion. In addition, children who are regularly transfused have significantly lower comorbidities.[37]

Although patients with VOC requiring hospitalization ≥3/year were found to have a significantly lower DBP, multivariate analyses of different factors did not reveal a significant association between VOC and both SBP and DBP. A finding similar to that reported by Lamarre et al in Guadeloupe, French West Indies.[38]

A small percentage (4.4%) of patients with SCA was reported to have prehypertension. Different studies have reported higher frequencies; Shatat et al.[30] reported pre-hypertension in 10%, and Becker et al.[18] in 17% of the patients with SCA, although both studies were conducted on adolescents with SCA. Bodas et al have reported prehypertension in 16.7% of patients with sickle cell disease aged 3-17 years.[39]

Another finding was the significant difference in renal function among patients with low SBP and DBP compared to those with pre-hypertensive state. Pre-hypertension among patients with SCA is mainly due to glomerulopathy characterized by glomerular hypertrophy, hypercellularity, mesangial proliferation and segmental glomerulosclerosis due to increased renal plasma flow, hypoxia, increased prostaglandin production and dilation of afferent glomerular arterioles that could reduce the

efficacy of diffusion due to the increased velocity. Arteriolar dilation will produce glomerular hypertension and systemic hypertension which is ultimately responsible for loss of filtration. Common mechanisms may also act such as growth factors or inflammatory cytokines. This could obstruct efferent arterioles, thus increasing intra-glomerular pressure and resulting in glomerular sclerosis.[40]

Limitations

Our study was limited by not including microalbuminurea testing on studied patients which is an important early marker of renal disease in these patients, and also not assessing the association between fetal Hb and BP which is a strong modulator of disease severity.

Conclusion

It can be concluded that age, growth measurements and anemia are independent risk factors that modulate BP among patients with SCA. Therefore, early nutritional support should be part of the treatment guidelines of these patients. Furthermore, routine BP measurements in pediatric patients with SCA is important for early detection of pre-hypertension to establish and receive effective treatment.

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