Arterial Blood Pressure in Children with Sickle Cell Anaemia and Controls: A Cross Sectional Study
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ABSTRACT

Background: Sickle cell anaemia (SCA) is a very common disorder among indigenous people of Borno and Yobe States in the North-eastern region of Nigeria. It is characterized by recurrent episodes of severe bone pain from occlusion of blood vessels by sickled red cells. Hypertension in children with sickle cell anaemia is rare and when present may be secondary to other disease process and more rarely may be essential hypertension. However, when hypertension occurs in SCA patients, it accelerates the progression of complications such as cerebrovascular accident and sickle cell nephropathy, hence the need to study the pattern of blood pressure in these patients. Early detection of hypertension can help in forestalling its progression and preventing its devastating complications such as cerebrovascular accident.

Objectives: To compare the arterial blood pressures of children with sickle cell anaemia in steady state with those of age and sex-matched healthy controls.

Methods: The study design was cross-sectional comparative. Minimum sample size of 54 was determined using Taylor’s formula. Subjects were recruited systematically by enrolling every other patient as they present at the Paediatric Haematology clinic. The controls were apparently healthy age and sex-matched haemoglobin AA children. Anthropometric parameters and the blood pressure were measured and recorded appropriately. Blood pressure was classified using published normative data.

Results: A total of 54 children with sickle cell anaemia in steady state and 159 normal children as controls were enrolled. The ages of both the SCA and controls ranged from 3 to 14 years, with median age of 8 years. Of the 54 SCA children 28 (52%) were males while 26 (48%) were females. Mean packed cell volume of the SCA children was 22 ± 3.5. Although 8 (14.8%) of the SCA children were hypertensive, there was no significant difference in the mean systolic blood pressure (96mmHg) of children with sickle cell anaemia compared to controls (99mmHg) P = 0.078 while, the mean diastolic blood pressure (65mmHg) of the control was significantly higher than that of SCA cohort (59) P ≤ 0.0001. Conclusion: Hypertension is not rare among children with sickle cell anaemia. This stresses the need regular BP recording during follow-up in order to prevent devastating events such as cerebro-vascular accident.

KEYWORDS: Arterial blood pressure, hypertension, sickle cell anaemia, children, North-Eastern Nigeria.

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Introduction
Sickle cell disease (SCA) is the most common inherited blood disorder of great public health importance worldwide. Sub-Saharan Africa accounts for three-quarters of the more than 300,000 SCA children born globally every year¹. It is a multisystemic disease affecting almost all organs of the body through the combined effects of chronic anaemia, recurrent infections, chronic hypoxia and repeated infarction². This
pathologic processes affect end organ functions with ultimate multi-organ failure. Hypertension in children with SCA is uncommon and may be secondary to another disease process or more rarely may be essential hypertension. Secondary hypertension is generally more common in children than in adults. Common causes of secondary hypertension in children include predominantly renal disease, endocrine disorders and coarctation of aorta that is amenable to surgery. However, some children and adolescents may have essential hypertension in which a cause of the disease is not identifiable. Essential hypertension in children has been demonstrated to correlate positively with family history of hypertension, obesity and low birth weight. Several researchers have documented that systemic blood pressure is generally lower in individuals with SCA compared to age and sex matched controls with normal haemoglobin. They attributed these findings to the prevailing chronic hypoxic state in SCA leading to vasodilatation and thus reduced peripheral resistance. Other factors attributable to low systemic blood pressure in children with SCA include salt loosing sickle cell nephropathy and the relatively large plasma volume resulting from low packed cell volume. With improved care and close routine follow up of children with SCA particularly in tertiary centres like ours, in addition to several strategies aimed at control of malaria and other infectious diseases; which are recognized important causes of mortality particularly in children with SCA, majority of these children are surviving into adolescent and adulthood. These young adults are likely to harbour several organs dysfunction owing to the underlying pathologic processes in SCA. Kidneys, the commonest cause of secondary hypertension in children, are one of the earliest organs affected in children with SCA. Both structural and functional abnormalities of the kidneys are recognized progressively beyond the age of five. The abundance of data on blood pressure pattern among these children and young adults with SCA documented low systemic blood pressure and thus, interval blood pressure check or cardiology referral is not part of the standard care protocol for SCA children and adolescents.

We thus, aim to determine the blood pressure pattern among children and adolescents with SCA and compare same with similar children without SCA in the North-eastern region of Nigeria. This may allow for early identification and prompt management of blood pressure abnormalities in children with SCA, thus, reducing the long term complications and improve their quality of quality of life.

Materials and Methods
This cross-sectional comparative study was conducted at the Paediatric Haematology Clinic and General Paediatric Outpatient Clinic of the University of Maiduguri Teaching Hospital (UMTH), over a period of six months, from January to June, 2016. The study population were known SCA children in steady state as defined by Akinola et al, on folic acid and proguanil aged between 3 and 14 years on routine follow up visit. Participants were recruited systematically by choosing alternate patients as they presented at the Clinic after meeting the inclusion criteria.

The controls were age and sex matched apparently healthy children with haemoglobin AA on follow up after recovery from minor ailments at the General Paediatric Outpatient clinic.
Ethical considerations
Approval was sought and obtained from the Hospital Research and Ethics Committee of the UMTH, written consent was obtained from the care givers after adequate education. Verbal assent was also obtained from children 7 years and older with unlimited liberty to deny consent or opt out of the study at any stage without any negative consequence. Those detected with hypertension were referred to Paediatric cardiology clinic for further evaluation and subsequent co-management.

Sample size: This was determined using Taylor’s formula, and P was taken from a previous study by Garlick et al from South-Western Nigeria who reported prevalence of 3%. Thus, 54 SCA children (cases) and 159 HbAA children (controls) were recruited.

Inclusion criteria: Children aged 3 - 14 years with SCA form the cases, apparently healthy non-SCA children age and sex matched form the control after consenting. Children below the age 3 years were not included because the study require measuring height of the subjects which children within this age group cannot cooperative to obtain accurate measurements. Even though length may be used for children in this age category, the procedure is cumbersome. Also, BP can vary by 40 – 50 mmHg in infants and young children following crying. Excluded were children whose parents/caregivers did not give consent to participate in the study. Information obtained from the cases include Biodata, history of previous episodes of crises and previous history of blood transfusion. The standing height in (cm) and weight in (kg) were measured using Wunder’s stadiometer fitted with a weighing scale. The body mass index (BMI) was calculated and classified using World Health Organization (WHO) growth charts.

Blood pressure of each subject was measured with Accoson’s mercury in glass sphygmomanometer using age appropriate cuffs (one which bladder covers two-third of the subject’s right arm in supine position). Systolic blood pressure was taken at the point at which the first Korotkoff sound was heard and the diastolic blood pressure at the point at which the Korotkoff sound became muffled. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were defined as normal between the 5th and the 90th percentile for age, sex and height. Hypertension was defined as BP greater or equal to the 95th percentile for age, sex and height percentile. Blood pressure was classified using published normative data (US).

Packed cell volume was determined for all the participants using capillary blood collected from a finger prick into a heparinized capillary tube after cleansing with alcohol. The PCV was read with the Hawksley haematocrit reader after centrifuging the capillary tubes.

Data obtained were analysed using Statistical Package for Social Sciences (SPSS) version 16 of 2008 (SPSS, Chicago, Illinois, USA). Means, standard deviation, frequencies and percentages, tables, graphs, and charts were used to present data. Paired t-test for comparing the means of two samples was used to test for significance of the differences between means of BP of SCA subjects and their controls, Chi-Square was used to compare categorical variables. Relationship were also explored using correlation and p value of 0.05 or less was considered significant at 95% confidence interval.
Results
A total of 54 children with SCA in steady state and 159 controls with haemoglobin AA were enrolled during the study period. The age and sex distribution of the study population is shown in table I.

Table 1: Age and sex distribution of the study population

| Age group (years) | SCA n (%) | CONTROL n (%) | TOTAL |
|------------------|-----------|---------------|-------|
|                  | Male      | Female        | Male  | Female |
| <5               | 6(21.4)   | 4 (15.4)      | 14(19.2) | 6(7.0) |
| 5-10             | 10(35.7)  | 14 (53.8)     | 27 (37.0) | 48(55.8)|
| >10              | 12(42.9)  | 8(30.8)       | 32 (45.2) | 32(34.5)|
| Total            | 28 (52)   | 26 (48)       | 73 (45.9) | 86(54.1)|

SCA=Sickle cell anaemia

Of the 54 SCA children 28 (52%) were males while 26 (48%) were females giving a Male: Female ratio of approximately 1.1:1. There was no significant difference in ages of males and females $X^2 = 3.437$ and $p=0.329$ in the SCA group.

The frequency distribution of the PCV of the SCA patients is as shown in figure 1, majority (53.7%) of the SCA patients had PCV between 21% and 25% while only 2 had PCV of >30%

![Fig. 1: packed cell volume distribution of children with SCA](image)

The mean blood pressure of the subjects and controls are shown in table III. Althou gh both the mean systolic and diastolic blood pressure of the control group were higher than those of the SCA group, only the diastolic blood pressure was significant ($P= 0.0001$). Eight (14.8%) of SCA children and none of the controls had blood pressures within the hypertensive range. The mean weight and height were also significantly higher in the controls than the children with SCA ($P= 0.0243$ and 0.0433) respectively.
Table 2: Mean blood pressure and anthropometric data of study population

| Parameters        | SCA        | Control    | P-value |
|-------------------|------------|------------|---------|
| Weight (kg)       | 21.98(7.39)| 25.90(11.93)| 0.0243* |
| Height (cm)       | 120.80(18.51)| 127.29(20.83)| 0.0433* |
| BMI (kg/m²)       | 14.91(3.12)| 15.07(2.87)| 0.7296  |
| SBP (mmHg)        | 95.56(10.55)| 99.11(13.38)| 0.0780  |
| DBP (mmHg)        | 59.48(8.39)| 64.96(8.57)| 0.0001* |

SCA = Sickle cell anaemia, SD = Standard deviation, BMI = Body mass index, SBP = Systolic blood pressure, DBP = Diastolic blood pressure. *p = <0.05

Only one child with SCA was overweight, and none was obese. While most 148 (84.9%) of the controls were underweight and none was overweight. The BMI of the SCA children and controls is shown in table III.

Table 3: Distribution of BMI of children with SCA and controls.

| BMI       | Frequency (%) | Haem AA |
|-----------|---------------|---------|
|           | SCA           | Controls|
| Underweight| 49 (90.7)    | 148(84.9) |
| Normal    | 4 (7.4)       | 11 (15.1)  |
| Overweight| 1 (1.9)       | 0 (0.0)    |

BMI = Body mass index (Kg/m²)

The SCA children with hypertension were significantly younger and shorter than those of them with normal blood pressure (p = 0.0112 and 0.0199) respectively. There was no significant difference in BMI between the hypertensive and normotensive SCA children Table IV.

Table 4: Association of clinical and laboratory parameters with the mean Systolic blood pressure in SCA Patients

| Factors        | Mean (SD) | Mean (SD) | t-value | p-value |
|----------------|-----------|-----------|---------|---------|
| Frequency      | Hypertensive | Normotensive |         |         |
|                | 8 (14.8%)  | 46 (85.2%) |         |         |
| Age in years   | 5.38 (1.061)| 8.80 (3.625)| 2.6301  | 0.0112* |
| PCV            | 22.00 (3.5857)| 22.00 (3.4189)| 0.0000  | 1.0000  |
| Weight in kg   | 17.88 (3.3568)| 22.696 (7.6837)| 1.7351  | 0.0886  |
| Height in cm   | 106.88 (5.939)| 123.20 (18.916)| 2.4028  | 0.0199* |
| BMI (kg/m²)    | 15.91 (4.2786)| 14.74 (2.9024)| 0.9763  | 0.3334  |

PCV = Packed cell volume, BMI = Body mass index. ∞ = summary, *p value <0.05
Discussion

In this study, we found a significantly lower mean diastolic blood pressure in SCA children compared to the control group. This agrees with the findings of previous studies; Ernst et al, Sergeant et al and Pegelow et al. Several reasons have been advanced on why the SCA children may have lower blood pressures. Firstly, the chronic hypoxia secondary to the chronic anaemic state in subjects with SCA, causes vasodilatation leading to lower peripheral resistance and hence lower systemic blood pressure. Furthermore, SCA children are known to have higher serum concentration of prostaglandin which is a potent platelets aggregation inhibitor and thus lowers peripheral resistance. Other factors attributable to low systemic blood pressure in children with SCA include salt losing sickle cell nephropathy, renal tubular damage with concentrating defects and increased renal tubular sodium and water excretion thus promoting lower arterial pressure.

In contrast to the prevailing overall lower mean blood pressure among the SCA children, 14.8% of them had elevated blood pressures. This finding is also in agreement with earlier reports of hypertension occurring in children with SCA. This high prevalence of hypertension stresses the need for routine measurement of blood pressure in children with SCA. These SCA children with hypertension were significantly younger when compared to those with normal blood pressure. Similar finding was reported from a study that used 24 hours ambulatory BP monitoring. Thus, it is unlikely that the finding from our study is due to ‘white-coat hypertension’. Higher PCV has been associated with higher BP in SCA from previous studies. However, there is no significant difference in PCV between hypertensive and normotensive groups in our study. The reason for high preponderance of hypertension in the younger age group may not be immediately clear, but may suggest that early phases of SCA nephropathy may be characterized by hypertension.

Anthropometric parameters in this study are similar to those described in most literature that patients with SCA have a growth delay which starts at the age of two years, and this affects weight more than the height and progresses through the adolescent years. Some reports demonstrated an association between elevated blood pressures and BMI. However, we did not find such association in our studies probably because BMI was low in virtually all groups as a lot of the enrollee are internally displaced from their homes due to the insurgency in the North-eastern part of Nigeria.

Other possible explanation for those findings is the fact that SCA patients have changes in plasma renin, endothelin and nitric oxide metabolites due to chronic vaso-occlusion with those changes affecting the balance between vaso constriction and vasodilatation, which is not usually seen in severely undernourished children.

Conclusion

In general, children with sickle cell anaemia have lower blood pressure when compared to those with HB AA. Hypertension may be more prevalent among the younger children with SCA. However, the identification of few SCA patients with hypertension stress the need to routinely measure the BP of children with SCA on follow up. Multi-centre studies with large sample size is desirable in Nigeria to evaluate BP in children and adolescents with SCA for detection of possible causes of hypertension and effective management to
avoid devastating events such as Cerebrovascular accident.

Acknowledgement
We are grateful to Professor Jose Pwavimbo Ambe for his willingness and immeasurable support in this work and Abdulmummini Garba of the Emergency Paediatrics side Laboratory of the University of Maiduguri teaching Hospital for running the PCVs of the SCA children.

Financial Disclosure: The authors declared that this study received no financial support.

Authorship contributions
Conceived and designed the experiments: Farouk AG and Ibrahim HU.
Performed the experiments: Farouk AG, Ibrahim BA and Ibrahim HU. Analyzed the data: Farouk AG, Elechi HA, Ibrahim BA and Idrisa JA.

Contributed materials/analysis tools: Farouk AG, Mustapha MG, Elechi HA, Idrisa JA and Ibrahim BA. Wrote the paper: Farouk AG, Mustapha MG, Ibrahim BA and Elechi HA.

Conflict of interest: None declared

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Cite this Article as: Farouk AG, Ibrahim HU, Ibrahim BA, Elechi HA, Idrsa JA, Mustapha MG. Arterial Blood Pressure in Children with Sickle Cell Anaemia and Controls: A Comparative Study. Bo Med J 2020;17(2): 1-9 Source of Support: Nil, Conflict of Interest: None declare