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# A STUDY OF GROWTH OF CHILDREN WITH SICKLE CELL DISEASE IN A SMALL DISTRICT IN CENTRAL INDIA- A CROSS SECTIONAL STUDY.

Paediatrics

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## ABSTRACT

**BACKGROUND:** Sickle cell disease is highly prevalent in some specific castes in some districts of Central India where the growth of child is often delayed. Few data are available in this context and on the issue using the World Health Organization growth norms. Hence we conducted the present study with the aim of describing the growth of affected children aged less than 5 years.

**METHODOLOGY:** An observational cross-sectional study was conducted from January 2019 to December 2019 for a period of 1 year, at the sickle cell centre in a tertiary care hospital in central India. The sample included 75 children with SCD aged 2 to 5 years old in steady state. Anthropometric measurements and socio-demographic data were collected and analyzed. All statistical tests were two-tailed with $p<0.05$ considered significant.

**RESULTS:** Median age of study population was 3.57 years. Low weight, height and weight for height Z-scores (<-2SD) were observed. Regression analysis indicated an association of low height-for-age and of low Body Mass Index (BMI)-for-age with age.

**CONCLUSION:** This study demonstrates unexpectedly lower mean Z-score for weight, height and weight for height than reported while using WHO norms.

## KEYWORDS

Sickle Cell Disease, Growth

## INTRODUCTION

Sickle Cell Disease (SCD) is the most prevalent genetic disease in the world [1, 2]. First described in the Nilgiri Hills of northern Tamil Nadu in 1952 [3] the sickle cell gene is now known to be widespread among people of the Deccan plateau of central India with a smaller focus in the north of Kerala and Tamil Nadu [4]. Extensive studies performed by the Anthropological Survey of India [5] have documented the distribution and frequency of the sickle cell trait which reaches levels as high as 35 per cent in some communities. Numerous acute and chronic complications are responsible for high morbidity and mortality in affected patients [1, 7]. Chronic complications include stunting and delayed puberty, particularly in homozygous patients, mainly because of increased basal metabolism related to hemolysis and chronic inflammation, endocrine disorders related to free iron toxicity on endocrine organs [7], multiple morbid episodes, micronutrient deficiency, [2, 8-14], and probably low socio-economic level [8, 14]. Although growth pattern in SCD has been studied, few African data are available [1, 15]. Most of the studies on growth used ethnical or specific growth charts [6, 9, 11-12]. We hypothesized that growth of children less than five, affected by sickle cell anemia, in a tertiary care center, may be near normal using WHO norms [16-18]. We therefore proposed to describe the anthropometric parameters of a population of children aged 2 to 5 years with homozygous sickle cell disease (Hb SS), according to the growth standards of the World Health Organization (WHO), then to identify the relationship between these parameters and severity criteria of the disease (clinical and hematological in a single center).

## METHODS

### TYPE OF STUDY:

It was a hospital based observational cross sectional study carried for 1 year (January to December 2019) in a single centre in a tertiary care hospital in Central India. Consecutive sampling included all children with homozygous SCD who came for routine consultation and whose parents or guardians gave their informed consent. We included patients aged 2 to 5 years in steady state.

Stunting, underweight, and wasting were defined by Z-score <-2 for height-for-age (HAZ), weight-for-age (WAZ) and BMI-for-age (BMI-Z), respectively. Stunting was considered mild for a Z-score between -1 and -2; moderate for a Z-score between -2 and -3 and severe for a Z-score <-3. Overweight and obesity were defined by IMC-Z respectively above +2 and above +3 Z-score.

### STATISTICAL ANALYSIS:

During the univariate analysis, we considered a p value significant <0.2. To control confounding factors and interactions between explanatory variables, we performed a multivariate analysis to high light the only factors influencing growth of our study population. The binary logistic regression allowed highlighting the relative risk factors (Odds Ratio) and the correlation was significant for a p value <0.05.

## RESULTS

**A total of 75 children were studied of** 34 were girls. The median age of patients was 3.57 years old. The diagnosis of Myelodysplastic Syndromes (MDS) was made at a median age of 13 months. More than half of the patients n=44 (58.67%) had already been transfused at least once. (Table 1) There was at least one hospitalization for severe vaso-occlusive crisis in 67 (89.3%) of them. Hematologic parameters of bone marrow activity and haemolysis were similar in girls and boys with the exception of leukocyte count, which was higher in boys (Table 2).

### ANTHROPOMETRIC PARAMETERS:

we found underweight in 3 (4%) patients, WAZ between -2 and -1 in 13 children (17.3%) and normal WAZ in 59 patients. WAZ projection on WHO curves was similar (Table 3). Stunting was found in 3 (4%) patients, emaciation in 22 (29%) and normal height in 49 patients (63.6%). The median size of the study population was -0.53 Z-score (-1.30, 0.57) (Table 3).

### RELATIONSHIP WITH THE SEVERITY CRITERIA:

the severity score of the disease was low in our study population. For a threshold of significance at 5%, no correlation was found between the severity criteria of the pathology and the growth indicators. The BMI seemed to be influenced by the increase in the number of transfusions, and the LDH levels. There were conflicting results regarding the correlation between platelet levels, reticulocyte levels and PAZ, between leukocyte levels and BMI, respectively (Table 4).

## DISCUSSION

We carried out this study in 75 children and evaluated their growth. Our goals were to describe height, weight, BMI, in light of WHO standards; and finally to look for a possible correlation between the manifestations of severity of the disease and these growth indicators. Our study was cross sectional, limiting analysis to growth velocity of each patient. In addition, patients enrollment was done in a specialized service, thus the results cannot be extrapolated to rural areas. Nevertheless, the results suggest that despite the difficult conditions of care in developing countries, children with sickle cell disease can have a similar growth to non-affected children.

**In our study we found that** the median age of our study was lower than that found by other authors because we chose to study exclusively under 5 years. This choice is due to a concern for the homogeneity of the study population and the desire to use WHO standards [16-20]. Our

population was similar to that of Silva *et al.* who studied children aged 5 months to 8 years [11]. The median age at diagnosis was 14 months close to that of Al Saqladi *et al.* (1 year) [9]. This age also differed from studies in western countries where neonatal screening is performed [10, 13, 14]. Newborn screening is not yet routinely done in our setting and diagnosis is evoked at the beginning of clinical manifestations. Disease was less severe in our study population probably due to young age as the trend of severity increase with age [13, 15]. Moreover, children were followed in a specialized care unit and this can also explain the few signs of severity observed.

**HEMATOLOGICAL PROFILE OF THE STUDY POPU LATION:**

the SS genotype was most represented in our study population. The other authors had a larger proportion of Sβ subjects [21, 22]. This difference could be explained by the fact that, genotypic diagnostic techniques are different. Indeed, the diagnosis of homozygous SCD in our study population was determined by HB electrophoresis at alkaline pH. This technique does not allow accurate quantification of Hb A2. The proportion of Sß could therefore be underestimated in our population. A high proportion of children had a high Hb F (>15%) with a median rate of 22%, above those of Al-Saqladi *et al.* (4.4%) [8, 12]. This difference in Hb F level could be explained by type of haplotypes [21]. In fact, there is a correlation between haplotype and hemoglobin F levels in one hand, haplotype and hemoglobin level on the other hand. The Benin haplotype, most found in our setting, is associated with a higher level of Hb F hemoglobin [21, 22]. The average hemoglobin level was 7.2g/dl, as in the under-5 population of Al-Saqladi *et al.* [12]. The mean free bilirubin level was approximately 2-fold higher than normal, as in the study populations of Al-Saqladi *et al.* In the study population of the latter, this rate increased significantly with age (p=0.005) [12]. The average levels of reticulocytes (241060/mm$^3$) and leucocytes (14525/mm$^3$) are about 1.5 and 2 times higher than the upper limits of normal values. The Al-Saqladi *et al.* study found similar levels for reticulocytes but lower for leucocytes [12].

**ANTHROPOMETRIC PARAMETERS OF THE STUDY POPU LATION:**

emaciation was found in 4% of the study population. This result is similar to that of Silva *et al.* [11] in Brazil and similar to the rate in general urban population (3.4%) of the same age [19]. Stunting was found in 4% of patients. This is greater than results from Silva *et al.* (1.4%) and Patey *et al.* [11, 20]. Optimal management performed in developed countries may explain this difference [16, 20] and also the type of study (case control in the Patey *et al.* study).

In addition, the Hb F level and the hemoglobin level could be correlated with the type of haplotype [21, 22]. Benin haplotye is associated with moderate forms of sickle cell disease expression and higher levels of HbF and Hb in carriers [21, 22]. This is different for the Bantu haplotype and the Arab-Indian haplotype. The mean LDH is not very elevated, which indicates that hemolysis is low. The low level of reticulocyte in our population, is suggestive of little erythropoietic bone marrow activity. This may also explain adequate growth in our study population. Indeed, glutamine, the most abundant amino acid in humans, whose endogenous production is reduced with age, is the "fuel" of choice for fast-growing cells such as reticulocytes. Based on these evidences, our study population has low energy expenditure and probably endogenous synthesis of glutamine enough to compensate resting energy expenditure and improve growth.

**CONCLUSION**

The present work shows that about 5% of the population of sickle cell children studied have growth impairment. Hence, WHO growth standards may be appropriate for sickle cell patients aged less than five.

**TABLES AND FIGURE**

**1. Table showing characteristics of study population:**

| VARIABLES | FREQUENCY |
|---|---|
| SEX: FEMALE/MALE | 34/41 |
| AGE IN YEARS (MEDIAN) | 3.57 (2.7 – 4.81) |
| AGE AT DIAGNOSIS IN MONTHS (MEDIAN) | 13 (7 – 28) |
| TYPE OF SCD N(%) | SS: 74 (98.7)<br>SB: 1 (1.3) |
| NUMBER OF VOC/YEAR (MEDIAN) | 2 (1 – 4) |
| NUMBER OF PREVIOUS TRANSFUSIONS | 1 (0 – 3.5) |
| FOLIC ACID: YES/NO (%) | 67 (89.3) / 8 (10.7) |
| HYDROXYUREA: YES/NO (%) | 8(10.7) / 67(89.3) |
| HYDRATION: NORMAL/INSUFFICIENT (%) | 44 (58.7) / 31 (41.3) |
| ANTIBIOTIC PROPHYLAXIS: YES/NO (%) | 58 (77.3) / 17 (22.7) |

**2. HEMATOLOGICAL PROFILE OF STUDY POPULATION**

| Variables* | Girls | Boys | p |
|---|---|---|---|
| Hb, g/dl | 7.5 (7-8.2) | 7.3 (6.3 -8.1) | 0.2 |
| MCV, fl | 79.40 (74-91) | 80 (74-88) | 0.8 |
| Leucocytes (x10$^3$mm$^3$) | 13.6 (11.4 -16.8) | 15.9 (13.3-17.5) | 0.02 |
| Platelets (x10$^3$ /mm$^3$) | 369.50 (286.50-523.50) | 336 (301 – 467) | 0.25 |
| Reticulocytes (x10$^3$/mm$^3$) | 281 (178.26-314.72) | 227.9 (195.04 – 361.21) | 0.6 |
| LDH (UI /L) | 1321 (1165 -1568) | 1650 (1159 – 1886.50) | 0.36 |
| Bilirubin (mg/L) | 19.7 (12.4 - 40) | 27.45 (14.85-34.75) | 0.8 |
| Hb F (%) | 21.9 (14.7 – 31.2) | 20.45 (14.5-25.25) | 0.7 |

**3. Mean Z-score of growth parameters of the study population**

| | | HEIGHT FOR AGE | | WEIGHT FOR AGE | | BMI FOR AGE | |
|---|---|---|---|---|---|---|---|
| Variables | n | Z-score | SD | Z-score | SD | Z-score | SD |
| All | 75 | -0.14 | 1.31 | -0.08 | 1.00 | -0.01 | 1.08 |
| Boys | 41 | -0.08 | 1.32 | -0.02 | 1.01 | 0.03 | 1.19 |
| Girls | 34 | -0.22 | 1.32 | -0.2 | 0.98 | -0.03 | 0.99 |
| Age (years) | | | | | | | |
| [2-3] | 29 | -0.34 | 1.48 | -0.13 | 1.15 | 0.11 | 1.16 |
| [3-4] | 17 | -0.31 | 1.33 | -0.25 | 0.89 | -0.08 | 1.07 |
| [4-5] | 29 | 0.17 | 1.12 | 0.06 | 0.89 | -0.08 | 1.02 |

**Table 4: Correlation between severity criteria and growth parameters (univariate analysis).**

| Correlation (p-value) | WAZ | HAZ | BMIZ |
|---|---|---|---|
| Age | -0,254 (0,001)* | -0,227 (0,002)* | -0,387 (0,000)* |
| VOC (number of hospitalisation) | -0,078 (0,369) | -0,098 (0,172)* | -0,056 (0,448) |
| Transfusion | -0,094 (0,418) | -0,110 (0,246) | -0,157 (0,096)* |
| Hb level (g/dl) | 0,0977 (0,378) | 0,0732 (0,446) | -0,025 (0,789) |
| Hb F (%) | 0,0355 (0,719) | 0,0589 (0,507) | 0,1063 (0,230) |
| MCV | -0,113 (0,307) | -0,115 (0,236) | -0,006 (0,947) |
| Leucocytes count | 0,0780 (0,482) | -0,070 (0,470) | 0,243 (0,011)* |
| Platelets count | 0,1837 (0,102)* | 0,0116 (0,906) | 0,0920 (0,350) |

| | | | |
|---|---|---|---|
| Reticulocytes count | 0,1903 (0,141)* | 0,0627 (0,580) | 0,221 (0,048)* |
| LDH | -0,032 (0,801) | 0,1059 (0,331) | -0,177 (0,101)* |
| Bilirubin | 0,0588 (0,660) | 0,0623 (0,597) | 0,0014 (0,990) |

*Pearson correlation significant when p value considered at 20%. Only variables with (*) were included in multivariate analysis

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