Foetal Haemoglobin and Disease Severity in Nigerian Children with Sickle Cell Anaemia

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Abstract. Background: Foetal haemoglobin (HbF) is a major modifying factor influencing sickle cell disease (SCD) severity. Despite this, HbF estimation is not routinely done in Nigeria. The relationship between HbF and SCD severity among affected children is also poorly studied. Methods: In this descriptive cross-sectional study, we determined the relationship between steady state HbF levels and disease severity of Nigerian children aged 1 – 15 years with homozygous SCD. For each child, the socio-demographic characteristics and SCD clinical severity were determined. The latter was assessed based on the frequency of significant painful episodes, blood transfusion, and hospitalisation in the preceding 12 months; lifetime cumulative incidence of SCD-related complications; the degree of splenic and hepatic enlargement; current haematocrit and leucocyte count. Foetal haemoglobin levels were quantified with high-performance liquid chromatography. Results: The mean HbF level of the 105 children with SCA was 9.9 ± 6.0%. Male had significantly lower mean HbF levels than females, 8.0 ± 5.6% vs. 12.2 ± 5.8% (p < 0.001). None of the children had severe disease. However, the 32 children with moderate disease had significantly lower mean foetal haemoglobin levels than the 73 with mild disease (7.7 ± 5.6% vs 10.8 ± 6.0% respectively). The mean HbF level was also significantly lower in children who had a history of acute chest syndrome and stroke compared to those without these complications, p = 0.002 and 0.010 respectively. Conclusion: Children with SCA who had a moderate disease and those with a history of life-threatening complications such as stroke and acute chest syndrome had significantly low HbF levels. Therefore, it is recommended that facilities for early quantification of foetal haemoglobin and HbF inducement were made available to reduce the morbidity and mortality among these children.

Keywords: Children, Sickle Cell Anaemia, Foetal Haemoglobin, Acute Chest Syndrome.

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Introduction. Globally, sickle cell anaemia (SCA) is the most common inherited haematological disorder.¹ It is found more frequently in sub-Saharan Africa, where it significantly contributes to the morbidity and mortality among children. It accounts for 5-16% of under-five mortality in the West African sub-region.² Nigeria has the largest burden of sickle cell anaemia worldwide with
about 150,000 affected babies being born annually. Affected children suffer varying morbidities contingent on the availability of appropriate care, necessary tools and drugs needed for management of the disease.

The presence of high foetal haemoglobin had been documented to ameliorate the disease severity in the western world where children with SCD are routinely given hydroxyurea in order to induce the production of foetal haemoglobin and reduce frequent crises. However, children in Nigeria and most other African countries still suffer devastating complications such as stroke, priapism, acute chest syndrome and deep sited infections like meningitis and cerebral abscess. Foetal haemoglobin level had been reported to be higher among Jamaican and Asian children with the consequent milder course of the disease. In Nigeria, there is a paucity of data on the influence of foetal haemoglobin levels on disease severity among children with SCA. Hence, this study aimed at determining the relationship between foetal haemoglobin level and disease severity among children with SCA in steady state.

Methods. A descriptive cross-sectional study was carried out in the Paediatric sickle cell disease clinic of the Wesley Guild Hospital unit, Obafemi Awolowo University Teaching Hospitals Complex, Ile Ife. A total of 105 children with SCA between age one and 15 years who were in steady state (no crisis, infection or fever for at least four weeks and no blood transfusion in the preceding three months) were consecutively enrolled. Children with other haematological disorders such as Glucose-6-Phosphate Dehydrogenase deficiency; and those with chronic liver, kidney and heart diseases were excluded. Children on hydroxyurea, those who did not give assent and those whose parent refused consent were not included. The study was approved by the Hospital Ethics/Research Committee (ERC/2013/11/12) and consent obtained from each parent/caregiver and assent from the children as appropriate.

A data proforma was used to obtain the socio-demographic characteristics such as age, sex and socio-economic class of participants as described by Oyedeji based on rank assessment of parental occupation and the level of education. The clinical severity of SCD was determined based on the number of admissions, blood transfusions and

significant painful crises (pain episode that requires a hospital visit and the use of analgesic) in the preceding 12 months and other complications present as described by Adegoke et al. Patients with a score of less than 8 were classified as having mild disease, 8 to 17 as moderate disease and greater than 17 as a severe disease from a total obtainable score of 34.

Venous blood sample was obtained and analysed for the complete blood count using ABX Micros ES 60 automated haemolysate and foetal haemoglobin levels using an automated BIO-RAD® D10 high-performance liquid chromatography (HPLC) machine at the Haematology Laboratory of the National Sickle Cell Foundation Lagos, Nigeria. Using the cut-off values of 10%, patients with HbF levels <10% were categorised as having low HbF while those with values ≥10% were categorised as having high HbF levels.

Statistical analysis. Data were analysed using the statistical package for the social sciences (SPSS) software for windows version 17.0. Means (± standard deviation, SD), median, proportions and percentages were determined as applicable. The means and standard deviations (±SD) were calculated for continuous variables while proportions and percentages were calculated for categorical variables. Categorical variables were compared with chi-squared or Fisher’s exact tests while continuous data were compared with independent sample t-test, Mann-Whitney U test or Analysis of variance (ANOVA) as indicated. The degree of correlation of continuous data was determined by Pearson’s correlation analysis. Logistic regression analysis was done to examine the independent effect of foetal haemoglobin on SCD severity. Statistical significance was established when the ρ-value was less than 0.05.

Results. Of the total 105 children with SCA studied, 59 (56.2%) were males with a M: F of 1.3:1. Their ages ranged from one to 15 years with a mean of 7.3 ± 3.6 years. Thirty-five (33.3%) were preschool (1 – 5 years), 50 (47.6%) were children aged 6 – 10 years and 20 (19.1%) were adolescents (>10 years). Forty (38.1%) of the population were from the lower social class (classes 4 and 5) while the middle and upper classes constituted 31.4% and 30.5% respectively.
year prior to recruitment. Also, 45 (42.9%) subjects had a history of dactylitis. The mean age at which they had the first dactylitis was 1.2 ± 1.0 years, ranging from three months to four years.

**Sickle cell disease severity.** The sickle cell disease severity score ranged from 0 - 14 with a mean score of 6.0 ± 3.2. Using a score of 0 - 7 for mild disease, 8 - 17 for moderate and >17 for severe disease, 73 (69.5%) had mild disease, 32 (30.5%) had moderate disease while none had severe disease.

The most common complication of SCA among the subjects was acute chest syndrome, seen in 19 (18.1%) of the children followed by osteomyelitis in 14 (13.3%). Other complications included stroke in 3 (2.9%), avascular necrosis of head of femur, chronic leg ulcers and priapism, 2 (1.9%) each.

**Foetal haemoglobin levels in the subjects.** The mean HbF level was 9.9 ± 6.0% with a range of 0.8 - 27.6%. Sixty-six (62.9%) had low HbF levels of less than 10% while 39 (37.1%) had high HbF value ≥10%. None had a 0% value.

**Relationship between socio-demographic characteristics and foetal haemoglobin.** Table 3 shows that male children had significantly lower mean haemoglobin F levels than females, 8.0 ± 5.6% vs 12.2 ± 5.8% (p < 0.001). Also, significantly higher proportion of males (78.0% vs. 22.0% of females) had HbF levels < 10%; $\chi^2 = 13.168$; $p < 0.001$. Additionally, the mean HbF across the age groups decreased with age and this was statistically significant ($\chi^2 = 3.851$, $p = 0.024$). The 39 subjects who had high HbF were significantly younger than those with low HbF (6.3 ± 4.1 years vs. 7.8 ± 3.3 years, $t = 2.150$, $p = 0.034$). Also, 19 (54.3%) of the 35 children who were 1 – 5 years compared with 20 (28.6%) of the 50 children with >5 years (i.e. age groups 6 - 10 years and 11 – 15 years) had high HbF levels, $\chi^2 = 6.608$, $p = 0.010$. There was a significant inverse correlation between HbF levels and age for both sexes, as shown in figure 1, $r = -0.3$, $p = 0.004$ for females, and $r = -0.3$, $p = 0.006$ for males.

On the other hand, the mean HbF levels were not statistically different in the socioeconomic classes ($p = 0.877$) and were not influenced by the frequency of pain crisis, blood transfusion and.

### Table 1. Socio-demographic characteristics of the 105 subjects.

| Socio-demographic characteristics | Subjects (105) | Percentages (%) |
|-----------------------------------|---------------|-----------------|
| Age in years                      |               |                 |
| Mean ± SD                         | 7.3 ± 3.6     |                 |
| Age group                         |               |                 |
| 1 – 5                             | 35            | 33.3            |
| 6 – 10                            | 50            | 47.6            |
| 11 – 15                           | 20            | 19.1            |
| Sex                               |               |                 |
| Male                              | 59            | 56.2            |
| Female                            | 46            | 43.8            |
| Socioeconomic class               |               |                 |
| I                                 | 9             | 8.6             |
| II                                | 23            | 21.9            |
| III                               | 33            | 31.4            |
| IV                                | 40            | 38.1            |
| V                                 | 0             | 0               |

Table 1 shows the age, sex and socioeconomic class distribution of the subjects studied.

**Clinical burden of the disease.** Table 2 shows that 89 (84.8%) experienced at least one episode of pain and 33 (31.4%) had more than three significant painful episodes requiring hospital visit and the use of analgesia in the 12 months preceding the study. Sixteen (15.2%) did not experience any significant painful episode in the year preceding the study. Fifty-one (48.6%) children required hospitalisation including two (1.9%) that required more than three admissions in the 12 months preceding the study. Twenty-one (20%) children were transfused at least once in the

### Table 2. Frequency of pain episodes, SCD-related hospitalisation and transfusion among the subjects in the 12 months preceding the study.

| Criteria                        | Frequency (%) |
|---------------------------------|---------------|
| Frequency of pain episodes      |               |
| 0                               | 16 (15.2)     |
| 1                               | 15 (14.3)     |
| 2 – 3                           | 41 (39.1)     |
| >3                              | 33 (31.4)     |
| Mean ± SD                       | 3.1 ± 3.0     |
| Median (Range)                  | 2.0 (0 – 15)  |
| Frequency of SCD-related        |               |
| 0                               | 54 (51.4)     |
| 1                               | 35 (33.3)     |
| 2 – 3                           | 14 (13.3)     |
| >3                              | 2 (2.0)       |
| Mean ± SD                       | 0.7 ± 0.9     |
| Median (Range)                  | 0.0 (0 – 4)   |
| Frequency of SCD-related        |               |
| 0                               | 84 (80.0)     |
| 1                               | 19 (18.0)     |
| 2 – 3                           | 2 (2.0)       |
| >3                              | 0 (0.0)       |
| Mean ± SD                       | 0.2 ± 0.5     |
Table 3. Relationship between foetal haemoglobin levels, socio-demographic and clinical burden of children with sickle cell anaemia.

| Demographic and clinical burden | Low HbF (N = 66) | High HbF (N = 39) | Pvalue | Mean ± SD HbF | Pvalue |
|---------------------------------|-----------------|-----------------|--------|---------------|--------|
| Age group (years)               |                 |                 |        |               |        |
| 1 – 5                           | 16 (45.7)       | 19 (54.3)       |        | 12.1 ± 6.1    |        |
| 6 – 10                          | 36 (72.0)       | 14 (28.0)       | 0.036***| 8.9 ± 5.5     | 0.024* |
| 11 – 15                         | 14 (70.0)       | 6 (30.0)        |        | 8.3 ± 6.2     |        |
| Gender                          |                 |                 |        |               |        |
| Male                            | 46 (78.0)       | 13 (22.0)       | <0.001 | 8.0 ± 5.6     | <0.001*** |
| Female                          | 20 (43.5)       | 26 (56.5)       |        | 12.2 ± 5.8    |        |
| Social class                    |                 |                 |        |               |        |
| I                               | 7 (77.8)        | 2 (22.2)        |        | 9.1 ± 6.3     |        |
| II                              | 15 (65.2)       | 8 (34.8)        | 0.527  | 10.0 ± 6.2    | 0.877* |
| III                             | 22 (66.7)       | 11 (33.3)       |        | 9.4 ± 5.6     |        |
| IV                              | 22 (55.0)       | 18 (45.0)       |        | 10.4 ± 6.4    |        |
| Frequency of pain episodes       |                 |                 |        |               |        |
| <3                              | 33 (57.9)       | 24 (42.1)       | 0.251  | 10.7 ± 6.5    | 0.147** |
| ≥3                              | 33 (68.8)       | 15 (31.2)       |        | 8.9 ± 5.3     |        |
| Frequency of transfusion         |                 |                 |        |               |        |
| <3                              | 65 (62.5)       | 39 (37.5)       | 0.334***| 9.9 ± 6.0     | 0.808** |
| ≥3                              | 1 (100)         | 0 (0)           |        | 8.4           |        |
| Frequency of hospital admission  |                 |                 |        |               |        |
| <3                              | 65 (64.4)       | 36 (35.6)       | 0.116***| 9.8 ± 6.1     | 0.347** |
| ≥3                              | 1 (25.0)        | 3 (75.0)        |        | 12.7 ± 3.3    |        |
| SCD severity                    |                 |                 |        |               |        |
| Mild SCD                        | 41 (56.2)       | 32 (43.8)       | 0.032  | 10.8 ± 6.0    |        |
| Moderate                        | 25 (78.1)       | 7 (21.9)        |        | 7.7 ± 5.6     | 0.013** |

* Analysed by ANOVA; ** independent sample t-test; *** Fisher’s exact test applied; The figures in parentheses are percentages of the total across each row.

Figure 1. Scatter plots showing the correlation between foetal haemoglobin levels and age of the patients in both sexes.

Relationship between foetal haemoglobin and disease severity. Those with moderate disease had significantly lower mean foetal haemoglobin levels than those with mild disease (7.7 ± 5.6% vs 10.8 ± 6.0% respectively; p = 0.013). Also, significantly higher proportion of subjects with moderate disease (56.2%) had HbF levels < 10% (χ² = 4.596, p = 0.032). On the other hand, more of the children with mild SCD severity (43.8%) than those with moderate disease (21.9%) had high levels of HbF (HbF ≥10%). Sickle cell disease severity score had significant inverse correlation with HbF levels (r = - 0.3, p = 0.002).

Relationship between socio-demographic characteristics and SCD severity. Disease severity worsens with age. Higher proportion of those >5 years, i.e. 27 (38.6%) of the 70 as against 5 (14.3%) of the 35 aged 1 – 5 years had moderate SCD severity. Those older than 5 years were 3.8 times more likely to have moderate disease severity than those aged 1 - 5 years, odd ratio = 3.8, 95% confidence interval = 1.3 – 10.9, p = 0.011. Also, more males, 39.0% (23/59) compared to 19.6% females (9/46) had moderate disease, OR = 0.4, 95% CI = 0.2 – 0.9, p = 0.032. Socioeconomic class did not significantly influence SCD severity. The proportions of children with mild disease who came from high social class (66.6%) and middle/low social classes (69.8%) were similar, OR = 0.9, 95% CI = 0.2 – 3.7, p = 1.000.
Table 4. Relationship between the mean foetal haemoglobin level and complications of sickle cell anaemia in the subjects.

| SCA complications | HbF Mean ± SD | t  | p value |
|-------------------|--------------|----|---------|
| Dactylitis        |              |    |         |
| Yes               | 9.9 ± 6.6    | 0.087 | 0.931 |
| No                | 9.8 ± 6.6    | -  |         |
| ACS               |              |    |         |
| Yes               | 6.9 ± 3.9    | -3.243 | 0.002 |
| No                | 10.5 ± 6.2   | -  |         |
| Osteomyelitis     |              |    |         |
| Yes               | 8.9 ± 5.1    | -0.661 | 0.510 |
| No                | 10.0 ± 6.2   | -  |         |
| Stroke            |              |    |         |
| Yes               | 5.6 ± 1.5    | -4.296 | 0.010 |
| No                | 10.0 ± 6.1   | -  |         |
| Priapism          |              |    |         |
| Yes               | 5.6 ± 2.1    | -1.025 | 0.308 |
| No                | 10.0 ± 6.0   | -  |         |
| Legulcer          |              |    |         |
| Yes               | 3.0 ± 2.3    | -1.676 | 0.097 |
| No                | 10.1 ± 6.0   | -  |         |
| AVN               |              |    |         |
| Yes               | 9.5 ± 10.0   | -0.246 | 0.806*|
| No                | 9.9 ± 6.0    | -  |         |
| Septicarthritis   |              |    |         |
| Yes               | 4.5          | -0.896 | 0.373 |
| No                | 9.9 ± 6.0    | -  |         |

ACS – acute chest syndrome; AVN – avascular necrosis; SCA – sickle cell anaemia

* Difference in the mean HbF for those with and without AVN was tested by Mann Whitney U test

Relationship between foetal haemoglobin and clinical characteristics. Table 4 shows that the mean foetal haemoglobin level was significantly lower in children who had a history of acute chest syndrome than those without this complication, (t = -3.243, p = 0.002). Similarly, children with a history of stroke had significantly lower HbF than those without the history of stroke (t = -4.296, p = 0.010). There was, however, no difference in the mean foetal haemoglobin levels of those with a history of osteomyelitis, septic arthritis, leg ulcer, priapism, avascular necrosis and dactylitis when compared to those without these complications. From table 5, higher proportion of children with low HbF had previous ACS ($\chi^2 = 5.033$, p = 0.025).

Multivariate logistic regression analysis. Logistic regression analysis was done to examine the independent effect of foetal haemoglobin on SCD severity. In the regression model, disease severity (dichotomised as mild or moderate) was taken as the outcome/dependent variable, and age group (1-5 vs >5 years), gender (male vs female), socio-economic class (high vs middle/low) and foetal haemoglobin (high vs low HbF) were all taken as the predictive/independent factors. None of these factors [age group, OR 0.3, 95% CI 0.1–1.0, p =

Table 5. Distribution of complications of sickle cell anaemia by the level of foetal haemoglobin.

| SCD complications | Patients with Low HbF | Patients with High HbF | Total | $\chi^2$ | p value |
|-------------------|-----------------------|------------------------|-------|----------|---------|
|                   | N = 66                | N = 39                 | N = 105 |         |         |
| Dactylitis        |                       |                        |       | 0.275   | 0.600   |
| Yes               | 27 (60.0)             | 18 (40.0)              | 45    |          |         |
| No                | 39 (65.0)             | 21 (35.0)              | 60    |          |         |
| ACS               |                       |                        |       | 5.033   | 0.025*  |
| Yes               | 16 (84.2)             | 3 (15.8)               | 19    |          |         |
| No                | 50 (58.1)             | 36 (41.9)              | 86    |          |         |
| Osteomyelitis     |                       |                        |       | 0.525   | 0.469*  |
| Yes               | 10 (71.4)             | 4 (28.6)               | 14    |          |         |
| No                | 56 (61.5)             | 35 (38.5)              | 91    |          |         |
| Stroke            |                       |                        |       | 2.838   | 0.092*  |
| Yes               | 3 (100)               | 0 (0)                  | 3     |          |         |
| No                | 63 (61.8)             | 39 (38.2)              | 102   |          |         |
| Priapism          |                       |                        |       | 1.880   | 0.170*  |
| Yes               | 2 (100.0)             | 0 (0)                  | 2     |          |         |
| No                | 64 (62.1)             | 39 (37.9)              | 103   |          |         |
| Legulcer          |                       |                        |       | 0.880   | 0.170*  |
| Yes               | 2 (100)               | 0 (0)                  | 2     |          |         |
| No                | 64 (62.1)             | 39 (37.9)              | 103   |          |         |
| AVN               |                       |                        |       | 0.140   | 0.709*  |
| Yes               | 1 (50.0)              | 1 (50.0)               | 2     |          |         |
| No                | 65 (63.1)             | 38 (36.9)              | 103   |          |         |
| Septicarthritis   |                       |                        |       | 0.934   | 0.334   |
| Yes               | 1 (100)               | 0 (0)                  | 1     |          |         |
| No                | 65 (62.5)             | 39 (37.5)              | 104   |          |         |

SCD – sickle cell disease; ACS – acute chest syndrome; AVN – avascular necrosis. The figures in parentheses are percentages of the total across each row. Fisher’s exact test applied.
0.050; gender, OR 1.9, 95% CI 0.7–5.0, p = 0.198; social class, OR 0.9, 95% CI 0.2–4.4, p = 0.947 and foetal haemoglobin, OR 1.8, 95% CI 0.6–5.2, p = 0.262] was found to be a significant independent predictor of SCD severity.

Discussion. Interest in foetal haemoglobin among patients with SCA has been on the increase in the last six decades during which its substantial protective effects on the timing and severity of the disease symptomatology and the development of multi-organ dysfunction became subjects of scientific research.\(^\text{11}\) However, in Nigeria, and indeed in most parts of sub-Saharan Africa, where the burden of the disease is highest, studies on foetal haemoglobin and its role on clinical manifestations and disease severity in children are scanty.

The clinical burden of SCA in our unit reflects the high burden of this disease in most parts of developing countries. In this study, about 85 percent of the children had experienced at least one significant pain episode necessitating hospital visit and use of analgesia; while about 20 percent were transfused and 50 percent were admitted for SCD-related morbidities in the twelve months preceding the study. These findings agree with the report by Brown et al\(^\text{12}\) among SCA children at the University College Hospital, Ibadan. It was also found in this study that about one-third of the subjects had more than three episodes of vaso-occlusive crisis and indeed this was responsible for most of the hospital admissions among them. This situation is consistent with the trend in some countries such as Britain and Saudi Arabia.\(^\text{3,14}\)

Although the frequency of pain and admissions have been reduced significantly in developed nations following the widespread use of hydroxyurea, this drug is not readily available, accessible and affordable in Nigerian and other sub-Saharan African countries where the principal precipitants of vaso-occlusive crises such as malaria and sepsis are still prevalent.\(^\text{15}\)

The mean HbF level of the children with SCA in this study is higher than what has been reported previously in most Nigerian studies. Isah\(^\text{16}\) in Sokoto found mean HbF level of 2.99 ± 5.16 percent as against 9.9 ± 6.0 percent in the present study. Also, the mean HbF level in this study is higher than 7.2 ± 5.0 percent reported by Tshilolo in Congo.\(^\text{17}\) This discrepancy may be due to the difference in the method of foetal haemoglobin estimation. The Betke method of alkali denaturation was used by Isah while HPLC which is a more sensitive method was used in the present study. Age difference might also account for the differences in the haemoglobin F level. For instance, relatively lower values were obtained in previous studies of adult sickle cell patients by Omoti in Benin (2.17 ± 1.81 percent), Durosinmi in Ife (4.26 ± 4.33 percent), Olaniyi in Ibadan (5.16 ± 4.04 percent) and Uko in Calabar (3.05 ± 1.61 percent).\(^\text{18-21}\)

A study among children with SCA in Uganda reported a mean HbF level of 9.0 ± 5.58 percent despite using alkali denaturation test.\(^\text{9}\) A higher value (12.2 ± 7.1 percent) was also reported in India by Rao et al.\(^\text{22}\) The reason for the differences may be due to the effect of various factors that influence foetal haemoglobin production in SCA individuals. One of the factors is beta gene haplotype of the disease. The Senegal, Saudi and Indian haplotypes are generally associated with higher levels of foetal haemoglobin and milder disease course while the Benin haplotype which is found commonly in our environment and the Cameroon haplotype are intermediate and of varying clinical manifestation. However, the Bantu haplotype is associated with severe disease and low foetal haemoglobin production.\(^\text{23}\) Another major factor that affects foetal haemoglobin level includes hydroxyurea, a ribonucleotide reductase inhibitor. The exact mechanism of how hydroxyurea increases HbF levels is not clear. It is frequently used in the western world in the management of children with sickle cell disease. Unfortunately, most children in Nigeria and other resource-poor countries in sub-Saharan Africa with the largest burden of the disease are not benefitting due to non-availability and/or unaffordability of the drug.

A recent in-vitro study highlighted a beneficial effect of Tropical almond (Terminalia catappa)in inducing HbF levels in erythroid progenitor cells.\(^\text{24}\) Possibly, a large-scale study and clinical trials on in-vivo use of this agent in children with SCA living in resource-poor countries may determine if it could be of comparative clinical utility. Currently, a Nigerian child who is using a 500mg capsule of hydroxyurea daily would spend close to 10 US dollars per month on HU therapy alone, in a country where more than 70 percent of the population is poor.
This present study found about two-thirds of our children with SCA (62.9 percent) had low foetal haemoglobin levels, and this was demonstrated in the pattern of the burden and complications seen in this study. We also observed that a significantly higher proportion of children with moderate disease severity compared to those with mild disease severity (78.1% vs 56.2%) had low levels of HbF. On the other hand, more of the children with mild SCD severity than those with moderate disease had high levels of HbF. A similar finding was reported by Mpalampa et al. among children with SCA in Uganda. Also, females in the present study had significantly higher HbF compared to males. This datum is similar to that found by Falusi et al. in a study of adult patients with SCA as well as in other studies by Mouele in Congo and Alsultan in Saudi Arabia. Olaniyi et al. in Ibadan, Nigeria found no difference in the HbF levels in both adult males and females with SCA. Falusi et al. attributed the finding to hormonal factor at puberty. However, in children, the exact reason for the higher levels of haemoglobin F among girls may not be explained by hormonal changes alone. The exact reason remains unclear, perhaps the X-linked co-dominant gene controlling the production of HbF may lead to a double dose of the gene as is the case for females unlike males, resulting in higher elaboration of the gene products, hence, higher HbF levels in females than males. The mean HbF was also found to be inversely related to age and significantly reduces with increasing age. This datum is similar to the finding of Adekile et al. among SCA individuals in Kuwait. It may be due to the relatively higher amount of F cells in the younger age group as observed by Akinsheyie et al.

We found that the mean foetal haemoglobin levels were significantly lower in children with moderate disease severity than those with mild disease and also in those who had a history of acute chest syndrome and stroke than those without these complications. Although there are no local data to corroborate or refute this observation, our findings are similar to the report by Mpalampa from Uganda. Increased polymerisation of the sickle cell haemoglobin in the presence of lower foetal haemoglobin may account for these unfavourable events among children with SCA. We did not find any relationship between foetal haemoglobin levels and previous history of priapism, osteomyelitis, septic arthritis and leg ulcer. Although a higher level of foetal haemoglobin has been found to be associated with fewer complications, the non-significant relationship between foetal haemoglobin and these other complications in this present study may be due to the fewer number of study participants with these complications.

Our study has some limitations. First, it is a cross-sectional study from a single centre. This type of study design is subject to recall, investigator and survival biases. In particular, information on the lifetime incidence of complications and frequency of significant pain episodes may have been subject to recall bias, despite the review of relevant medical charts in addition to clinical histories to obtain that information. Secondly, the relatively small number of patients studied could also affect generalisability of our findings. Future studies should be multi-centred, longitudinal in design and involve a larger population.

It is concluded that foetal haemoglobin level has a significant inverse relationship with disease burden and severity among children with sickle cell anaemia. Advanced age and male gender were also significantly related to low foetal haemoglobin levels in these children. Therefore, it is recommended that facilities for early and regular quantification of foetal haemoglobin be made available, and access to HbF inducing agents, specifically hydroxyurea encouraged in order to reduce the morbidity and mortality among these children.

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