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Comparison of Pubertal Development between Subjects with Sickle Cell Anaemia and Individuals with Normal Haemoglobin in South-western Nigeria

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Abstract

Background

Sickle cell disease (SCD) is a haemoglobinopathy which results from a point mutation in the β-globin gene of haemoglobin. It is a disease of global health concern, with significantly higher morbidities and mortalities in low-income countries. Although an increasing proportion of affected children now survive into adulthood in these countries, there remains a significant risk of long-term complications such as endocrine disorders. Previous studies have reported delayed pubertal development in SCD, there is, however, paucity of recent studies on pubertal development, and the factors that influence the attainment of puberty, in SCD patients in Nigeria.

Methods

The present study was a cross-sectional study involving 139 eligible subjects with sickle cell anaemia (SCA), aged 6 to 18 years, and 133 individuals with haemoglobin AA (HbAA). Pubertal staging of subjects and controls was done using the Tanner criteria, while blood samples were obtained from individuals who had attained puberty for testosterone, estradiol, follicle stimulating hormone (FSH) and luteinizing hormone (LH). Hormonal assays were performed using Rayto RT 6100^{R} ELISA microplate reader for FSH and LH, and Rapid^{R} Labs ELISA kits for oestradiol and testosterone.

Results

Female SCA subjects attained thelarche at a mean age of 12.3±1.71years compared to 9.8±1.86 years in controls; adrenarche at 13.2±1.81years against 10.9±1.67years in controls, and menarche at a mean age of 14.1 ± 1.7years compared to 12.3±1.3years in controls. Males with normal haemoglobin also attained puberty earlier than SCA. Mean LH and FSH were higher in SCA subjects (8.29±33.75mIu/ml and 6.81±10.61mIU/ml respectively) compared to mean values of 3.17±5.0mIU/ml and 3.85±3.88mIU/ml respectively in controls. Estradiol and Testosterone levels were however higher in the control group.

Conclusion and recommendation

The present study confirms delayed onset of puberty in patients with SCA compared with HbAA controls. Screening for endocrine complications should therefore be incorporated into the comprehensive care model for SCA for early detection of impairments and prompt institution of appropriate interventions.

Keywords: Pubertal Development, Sickle Cell Anaemia, Haemoglobin AA, Hormonal Profile

Introduction

Sickle cell disease (SCD) is a haemoglobinopathy which results from a point mutation in the β-globin chain of the haemoglobin molecule [1]. This mutation results in replacement of glutamic acid valine at the sixth position of the amino acid sequence of the β-globin chain ultimately leading to the formation of sickle haemoglobin (HbS) [1]. The presence of HbS results in a conformational change in the haemoglobin tetramer which causes deoxygenated HbS molecules to interact with each other to form the rigid polymers that give RBCs the characteristic sickle shape. Inheritance of homologous HbS result in SCA [1].

Sickle cell disease is a disorder of global health concern [2, 3], with a significantly higher morbidity and mortality burden borne by low-income countries in Africa, Middle East, India, South and Central America, the Caribbean Islands and some parts of the Mediterranean [3]. The disorder is responsible for 5% of under-five mortality on the African continent, more than 9% of which occur in west Africa, while sickle cell related deaths among under-five children in west-African countries is estimated to be 16%

[4]. Although an increasing proportion of affected children now survive into adulthood in these countries due to improvement in emergency and routine care, there remains a significant risk of long-term sickle cell-related complications [4] which include endocrine disorders.

The pathophysiology of endocrine organ dysfunction in patients with SCA remains unclear [5]. However, iron deposition due to recurrent and frequent transfusions, ischemia due to vaso-occlusive crises and the role of inflammatory mediators during ischaemia, have all been proposed to play a role in sickle cell related endocrine dysfunction [5]. Additionally, chronic haemolytic anaemia associated with SCA probably contributes to impaired growth, delayed sexual maturation and malnutrition. With high prevalence of malnutrition in Africa, it has been suggested that this may be an important risk factor for delayed growth and puberty in children with SCA [6].

Previous studies [5, 7, 8] have suggested an impairment of growth and pubertal development in SCA. Some studies [7, 8] have reported a pubertal delay by an average of approximately two years in both boys and girls with SCA, while menarche may be delayed by two to three years. There is however a paucity of recent data on pubertal development and the associated contributory factors among SCA patients in Nigeria. Some of the available studies [9] from this region were restricted to male SCA subjects, while the others that involved both sexes were carried out over two decades ago [10]. The present study was therefore conceived to compare pubertal development in SCA subjects with matched individuals with HbAA, as well as to identify factors that may contribute to prevailing patterns in both groups in our environment.

Materials and Method

A cross-sectional study of SCA and HbAA patients attending specialist paediatric haematology clinics and paediatric out-patient departments of public and private hospitals in Ogun state, Nigeria was conducted over a period of eight months. Subjects were 139 individuals with SCA in their steady states, aged 6-18years, while 133 individuals with HbAA served as controls. Steady state was defined as the absence of any of the sickle cell crises, hospital admission or blood transfusion in the preceding four weeks prior to enrolment. Age and sex-matched, apparently healthy, individuals with HbAA phenotype served as controls. Subjects or controls previously on corticosteroids, androgens, or any other drug with androgen-like effects that may affect growth and development, and those with chronic illnesses like diabetes mellitus, hypertension, bronchial asthma, cardiac or/ and renal disease were all excluded from the study.

Participants were recruited from four health facilities spread across two Local Government Areas (LGA) of the state. The two LGAs (i.e. Abeokuta-south, Ijebu-ode) were selected by simple random sampling method from the three LGAs in the state with dedicated Sickle cell clinics. Ijebu-ode had only one health facility with a specialist clinic, while Abeokuta-south had three of such centers. Participants were proportionately, consecutively recruited from the four study sites till the estimated sample size was reached.

Approval for the study was obtained from the human research ethical committees of the participating institutions prior to the commencement of the study. Written consents were obtained from parents or caregivers, and verbal assents from patients aged 7 years and above prior to their enrolments for the study. Refusal of consent did not interfere with the care received by patients, while participation did not pose any risk of harm to the subjects. Privacy and confidentiality were always ensured while sensitive examinations were carried out with chaperons in attendance, and by a gender-matched physician when feasible.

A semi-structured researcher administered questionnaire was used to record socio-demographic, clinical and laboratory parameters of subjects and controls. Socio-economic status was done using the Oyedeji social classification [11].

For pubertal staging: Each patient was examined in the presence of a chaperon appropriate with the gender and correlated with the Tanner staging criteria for pubertal for either sex. Tanner stage 1 represents the pre-pubertal stage, while stage 5 indicates full maturity. Pubic hair distribution was assessed by inspection for both gender, breast development in girls was assessed by inspection and palpation, while testicular volume was measured using the Prader Orchidometer and correlated with the pubertal stage. Testicular volume of 4mls was taken to indicate onset of puberty. Participants with Tanner stage 2 or for breast (B2) and/or pubic hair (PH2) development in females or genital (G2) and/or pubic hair (PH2) development in males were classified as having attained puberty.

Blood sampling and procedure: Blood samples for haemoglobin electrophoresis were obtained from participants with unknown haemoglobin phenotypes prior to recruitment, while those who had prior documented evidence of their haemoglobin phenotype as either genotype AA or SS were directly recruited. Four milliliters of venous blood was obtained after adequate skin preparation from participants in puberty (at least Tanner stage 2) into plain sample bottles. The samples were then centrifuged, and the serum obtained stored at temperature of -20^{o}C until analysis was performed. Hormonal assay was carried out using Rayto RT 6100^{R} Elisa microplate reader (manufactured by Rayto Life and Analytical Sciences Co., Ltd China) for FSH and LH, while oestradiol and Testosterone were assayed using Rapid^{R} Labs Elisa kits (stored at 2-8^{o} C).

Data analysis

Data was analysed using Microsoft Excel^{R} 2010 (Microsoft Corporation SP2 software Microsoft office 2010 professional plus (PC) Intel Corporation's 386 microprocessor Redmond, Washington, USA) and Statistical package for social statistics SPSS 22.0(SPSS Inc Illinois, USA). Numerical data were described in terms of means, range and standard deviation. Categorical data was described in proportions. The mean ages at puberty and menarche between the two groups were compared using t- test for independent samples. Correlation analysis was also done using the Pearson's correlation test. Statistical significance was set at 95% CI ($p = 0.05$).

Logistic regression was used to determine the combined association between independent variables like age, socioeconomic class, family type, family size, frequency of crises, admissions and blood transfusion and the dependent variable of having attained puberty. The statistical significance of the effects in these models was assessed by using odd ratio tests.

Results

Socio-demographic characteristics of study population

A total of 309 patients were recruited; 37 were excluded due to incomplete data while 272 completed the study. Subjects

were 139 (51%) SCA patients while 133 (49%) age and sex-matched individuals with haemoglobin AA served as controls. The mean age for the subject group was 10.62±3.07years while for the control group was 10.20±2.98. One hundred and twenty-six (46.3%) of the participants were male, 146 (53.7%) were female, M: F = 1:1.1. Most 146 (54%) of the families belonged to socioeconomic classes II and III. However, most of the parents for the control were from socioeconomic class 1 and 11 while for the subject group 105 were from socioeconomic class 111 and 1V. (Table 1).

Table 1: Socio-demographic characteristics of subjects and controls

Variable	HBSS Frequency (%) n = 139	HBAA Frequency (%) n = 133	Total (Frequency %) n = 272
Age group(yrs.)			
Preadolescent	53(38.1)	60(45.1)	113(41.5)
Early adolescent	49(35.3)	38(28.6)	87(32.0)
Mid adolescent	32(23.0)	31(23.3)	63(23.2)
Late adolescent	5(3.6)	4(3.0)	9(3.3)
Sex			
Male	65 (47.0)	61 (45.9)	126 (46.3)
Female	74 (53.0)	72 (54.1)	146 (53.7)
School type			
Public	59 (42.4)	30 (22.6)	89 (32.7)
Private	80 (57.6)	103 (77.4)	183 (67.3)
Ethnic group			
Yoruba	133 (95.7)	123 (92.5)	256 (94.1)
Igbo	5 (3.6)	8 (6.0)	13 (4.8)
Hausa	0 (0.0)	1 (0.8)	1 (0.4)
Non-Nigerian	1 (0.7)	1 (0.8)	2 (0.7)
Family type			
Monogamy	87 (62.6)	114 (85.7)	201 (73.9)
Polygamy	52 (37.4)	19 (14.3)	71 (26.1)
No of siblings			
1-4	77 (55.3)	107 (80.6)	184 (67.6)
5-8	54 (38.8)	22 (16.6)	76 (27.9)
9-12	8 (5.7)	2 (1.5)	10 (3.6)
>12	0 (0.0)	2 (1.5)	2 (0.8)
Socioeconomicclass			
I	11 (7.9)	53 (39.8)	64 (23.5)
II	21 (15.1)	51 (38.3)	72 (26.5)
III	57 (41.0)	17 (12.8)	74 (27.2)
IV	48 (34.5)	12 (9.0)	60 (22.1)
V	2 (1.4)	0 (0.0)	2 (0.7)

Attainment of pubertal development in SCA compared to non-SCA control population

Forty-four (31.7%) of the subjects group had attained thelarche/gonadarche, while 79 (59.4%) of the control group had attained thelarche/gonadarche, as seen in Fig 1.

Thirty-two (23%) of the SCA group had attained adrenarche, while 61(45.9%) of the control group had attained adrenarche as shown in Fig 2.

Majority of the participants in both groups were in the stage 1 of pubertal development for genital/breast and pubic hair development; most of the males who had attained puberty were in stage 2, while most of the females were in stage 3 of pubertal development. (Tables 2a and 2b).

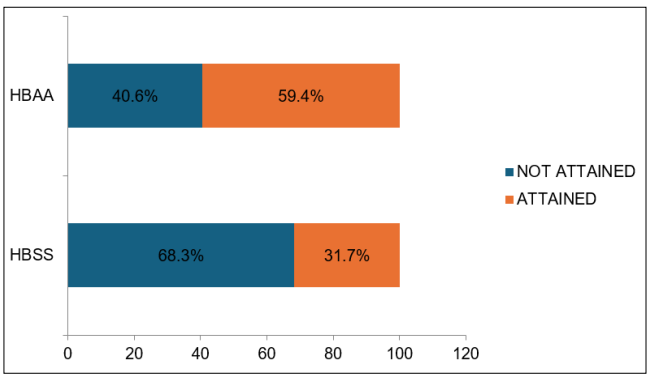

Fig 1: Comparison of Thelarche/Gonadarche status among Sickle cell subjects and normal haemoglobin patient

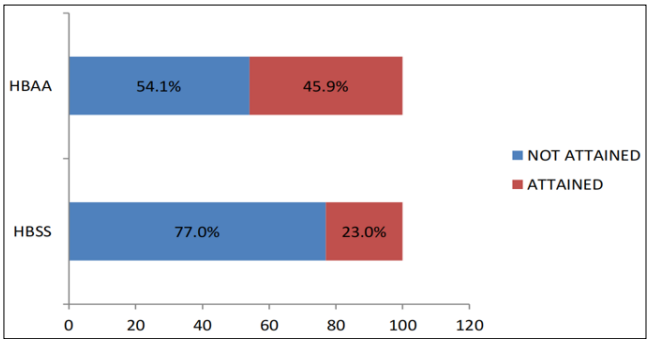

Fig 2: Comparison of pubarche status among sickle cell subjects and normal haemoglobin patient

Table 2a: Proportion of the male participants and pubertal staging

Variables	Genital stage N (%)	Pubic hair stage N (%)
Stage 1		
HbSS	47(33.8)	55(41.4)
HbAA	30(22.6)	45(33.8)
Stage 2		
HbSS	8(5.8)	4(2.9)
HbAA	18(13.5)	5(3.8)
Stage 3		
HbSS	4(2.9)	4(2.9)
HbAA	6(4.5)	5(3.8)
Stage 4		
HbSS	4(2.9)	1(0.7)
HbAA	5(3.8)	5(3.8)
Stage 5		
HbSS	2(1.4)	1(0.7)
HbAA	2(1.5)	1(0.8)

Table 2b: Proportion of female participants and pubertal staging

Variables	Breast stage N (%)	Pubic hair stage N (%)
Stage 1		
HbSS	47(33.8)	49(35.3)
HbAA	24(1.81)	27(20.3)
Stage 2		
HbSS	4(2.9)	10(7.2)
HbAA	9(6.8)	11(8.3)
Stage 3		
HbSS	12(8.6)	8(5.8)
HbAA	16(12.0)	10(7.5)
Stage 4		
HbSS	6(4.3)	5(3.6)
HbAA	11(8.3)	10(7.5)
Stage 5		
HbSS	5(3.6)	2(1.4)
HbAA	12(9.0)	14(10.5)

Age at the different Tanner stages for breast (B)/ genital (G) and pubic hair (PH) development were compared for sickle cell anaemic (subject) against normal haemoglobin AA (control) populations (Tables 3a & 3b)

From Table 3a, mean age for the onset of breast development (B2) in the female SCA group was 12.3±1.71years while it occurred earlier in the control group at a mean age of 9.8±1.86 years. The same pattern was observed for pubic hair development, and the differences were statistically significant. Mean age for onset of thelarche was delayed by two years while the mean age at completion was delayed by less than a year in the patients with sickle cell anaemia.

From Table 3b, mean age of onset of genital development in the male control group was 10.0±1.65years, while for the SCA group gonadarche occurred at a later age of 12.4±1.51years. The same pattern was demonstrated for pubic hair development in males and these differences were statistically significant. Overall, the mean age for onset of puberty was delayed by over two years for genital development, and over one year for pubic hair development in the SCA group. Considering age at completion of pubertal development, genital development was delayed by three years, while pubic hair development by four years in subjects with SCA. The age differences at completion of puberty were however not statistically significant.

Table 3a: Comparison of mean Age at Tanner stages for breast and pubic hair development in females with and without SCA

Breast stage (B)	Non-SCA mean±SD	SCA mean±SD	p-value	Pubic hair (PH)	Non-SCA mean±SD	SCA mean±SD	p-value
1	7.7±1.40	9.0±2.16	**0.009***	**1**	7.7±1.43	9.1±2.13	**0.005***
2	9.8±1.86	12.3±1.71	**0.045***	**2**	10.9±1.67	13.21±1.81	**0.010***
3	10.8±1.34	13.3±1.37	**0.000***	**3**	11.0±1.73	14.1±1.25	**0.000***
4	13.8±0.87	15.0±1.10	0.051	**4**	12.9±2.23	15.0±1.88	0.095
5	14.8±2.04	15.4±2.07	0.611	**5**	14.7±1.49	16.5±2.12	0.148

*P < 0.05 (t-test independent sample), values expressed as mean age (n) and standard deviation (SD)

Table 3b: Comparison of mean Age at Tanner stages for genital and pubic hair development in males with and without SCA

Genital stage(G)	Non-SCA mean±SD	SCA mean±SD	p-value	Pubic hair (PH)	Non-SCA mean±SD	SCA mean±SD	p-value
1	7.6±1.50	9.2±2.28	**0.002***	**1**	8.32±1.88	9.7±2.55	**0.004***
2	10.0±1.65	12.4±1.51	**0.002***	**2**	11.6±0.89	13.0±0.82	**0.046***
3	12.5±1.05	13.3±0.96	0.286	**3**	13.2±1.30	14.5±0.58	0.109
4	14.4±0.55	15.0±1.41	0.407	**4**	13.8±1.30	17.0±0.11	**0.001***
5	13.5±0.71	16.5±2.12	0.20	**5**	14.0±1.60	18.0±1.30	0.092

* P < 0.05 (t-test independent sample), values expressed as mean age (n) and standard deviation (SD)

Age at menarche

Mean age at menarche was significantly greater in the subjects with SCA; 11 (7.9%) of these subjects attained menarche at a mean age of 14.1±1.7years compared to 23 (17.3%) of the control group who attained at a mean age of 12.3±1.3years**,** indicating statistically significant 2-year delay in attainment of menarche in subjects. The pattern of attainment of puberty in subjects and controls is illustrated in Fig 3.

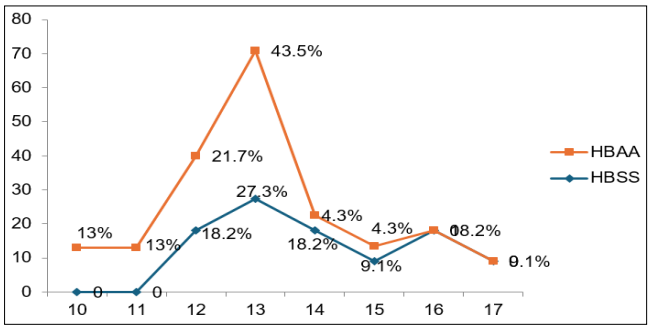

Fig 3: Age at menarche of the respondents

Comparison of hormonal assay variables of SCA patients with control group

Hormonal assay results for female subjects with SCA and the control group is shown in Table 4a. Mean LH and FSH levels were statistically higher in subjects with SCA **(p=0.000),** while oestradiol levels were significantly higher in the control group **(p-0.000).** Testosterone levels were also higher in the control group although this difference was not statistically significant.

For the males, mean LH and FSH levels were also both significantly higher in the SCA group, while mean oestradiol and testosterone levels were both significantly higher in the control group (Table 4b).

Table 4a: Mean values of hormonal assay for females

Variables	HbSS mean±SD	HbAA mean±SD	r	Sig.(2-tailed)
LH (mIU/l)	12.80±43.27	4.15±5.87	0.894**	**0.000***
FSH (mIU/l)	7.94±13.11	4.13±3.60	0.889**	**0.000***
Estradiol (pg/ml)	17.82±15.07	81.56±86.28	0.902**	**0.000***
Testosterone (ng/ml)	0.84±0.24	0.25±0.25	0.407*	**0.035 ***

r= Pearson correlation coefficient, ** Correlation is significant at the 0.01 level (2-tailed). * Correlation is significant at the 0.05 level (2-tailed). SD standard deviation.

Table 4b: Mean values of hormonal assay for males

Variables	HbSS mean±SD	HbAA mean±SD	r	Sig.(2-tailed)
LH (mIU/l)	1.62±1.98	1.54±1.95	0.960**	**0.000***
FSH (mIU/l)	4.97±3.95	3.40±4.33	0.933**	**0.000***
Estradiol(pg/ml)	12.82±20.13	20.19±15.92	0.998*	**0.041***
Testosterone(ng/ml)	0.48±0.91	20.19±0.80	0.781**	**0.000***

r= Pearson correlation coefficient, ** Correlation is significant at the 0.01 level (2-tailed), *Correlation is significant at the 0.05 level (2-tailed). SD standard deviation

Relationship of Socio-demographic parameters and disease severity indices to onset of puberty (Tanner stage 2 or more) in children with sickle cell anaemia

Relationship between socio-demographic parameters, disease severity indices and pubertal development (Tanner stage 2) was considered in a Univariable logistic regression analysis as shown in Table 5a and 5b. In the Univariable analysis, age, socio-economic status of parents, family setting, family size, maternal menarcheal age and nutritional status were positively associated with pubertal development in girls. However, this was only statistically significant for age; for every increase in age by one year there was an approximately four-fold likelihood for a girl to attain puberty.

Table 5a: Factors associated with onset of puberty (Tanner stage 2 or more) in girls

	Univariable Regression		
Term	**Odds ratio**	**95% CI**	**p-value**
Age	3.5	1.83-6.78	**0.000***
Socioeconomic status	1.5	0.75-2.90	0.261
Family type	1.8	0.21-1.46	0.234
Family size	1.1	0.86-1.29	0.597
Maternal menarcheal age	0.4	0.13-1.06	0.967
Nutritional status	0.5	0.25-1.11	0.127
No of crises/year	1.2	0.72-1.84	0.547
No of admission/year	1.0	0.24-4.19	0.991
No of blood transfusion/year	0.3	0.09-1.10	0.069

**P<0.05 is significant*

Advanced age, socio-economic status of parents, family setting, and family size, were positively associated with pubertal development for boys in the Univariable analysis (Table 5b). Increasing number of blood transfusion and crises per year had a negative association with pubertal development. However, in all, only increasing age and family size were found to be statistically significant. Boys were 4

times more likely to attain puberty for every increase in age by one year.

Table 5b: Factors associated with onset of puberty (Tanner stage 2 or more) in boys

Variable	Univariate	Regression	
Term	Odds ratio	95% CI	p-value
Age	4.0	1.74-8.98	0.001*
Socioeconomic status	1.2	0.62-2.46	0.548
Family type	1.1	0.36-3.58	0.831
Family size	1.4	1.02-1.82	0.037
No of crises/year	1.7	0.92-3.26	0.087
No of admission/year	0.4	0.04-2.93	0.338
No of blood transfusion/year	1.2	0.46-3.22	0.687

*P<0.05 is significant

Discussion

The present study set out to compare the pubertal development of children with sickle cell anaemia with that of matched individuals with normal haemoglobin. Delay in onset and completion of puberty was evident in subjects with SCA in this study. Although most of the participants (41.5%) from both groups were in the pre-adolescent age bracket, the number of participants from the control group who had attained puberty was higher (59.3%) than in SCA group 45(32.4%). In females with SCA, there was a delay of 2.5 years for thelarche, and 2.2 years for adrenarche, while completion of puberty was also delayed by less than a year. For the male subjects, the mean age for the onset of puberty was delayed by more than 2 years for genital development and more than 1 year for pubic hair development. Completion of puberty was delayed by 3 years for genital development and 4 years for pubic hair development.

The findings from the present study are comparable to those from previous similar studies from Africa [10, 12-14]. Soliman *et al* [14] in a comparative study in Alexandria, Egypt found that 66% of females with SCA had delayed breast development with a mean age of thelarche at 13.5 years, while the mean age at menarche was 15.6 years. As for the males, 25% of boys with SCA over the age of 14 years had absent testicular development. Males with SCA and delayed pubertal development have significantly smaller testicular volume and lower testosterone concentrations [12, 14]. These findings were corroborated by other studies by Abbiyesiku *et al* [10] and Modebe *et al* [12] in Nigeria, as well as Jacob *et al* [13] in Tanzania.

Similar studies from high income countries have also reported delayed pubertal development in patients with SCA [8, 15]. A prospective study by Zemel *et al* [8] in United States of America found delay in puberty when compared to healthy patient which was more pronounced in male subjects, while the females were observed to recover with the progression of puberty [8]. Platt *et al* [15] also in U.S.A also observed similar patterns of delayed puberty amongst African American children with SCA. These findings suggest that other mechanisms aside under-nutrition and low socioeconomic status, both of which are common amongst SCA patients in LMICs, may contribute to delayed puberty in SCA.

Additionally, the hormonal profiles of the subject group in this study demonstrated higher levels of LH and FSH when compared to controls. However, the sex hormones values were higher in the control group. This implies that delayed puberty in patients with SCA is due to primary hypogonadism. This is consistent with previous findings by various authors [10, 16, 17]. El-Hazmi *et al* [17] in Saudi Arabia also reported gonadal hypofunction in SCA patients, with those with severe forms of the disease demonstrating more frequent abnormalities of LH, FSH, cortisol and testosterone in comparison with patients with mild disease.

The aetiology for hypogonadism in SCA is however unclear; several causes, including primary testicular failure, hypothalamic and/or pituitary dysfunction, zinc deficiency, and constitutional delay of puberty, have been proposed. Recurring episodes of intravascular sickling, vaso-occlusion, and infarction, as well as tissue hypoxia associated with chronic anaemia, are postulated to be responsible for the testicular failure in SCA [5]. Iron overload from chronic haemolysis and blood transfusions, as well as zinc deficiency resulting from urinary losses are also common in subjects with SCA, and contribute to endocrine dysfunction and pubertal delay in this group of patients. Prasad *et al* [18] suggested that zinc deficiency in adolescent patients with SCA was associated with growth retardation and hypogonadism in males. Although zinc supplementation in their study population improved testosterone levels and longitudinal growth, the underlying mechanism remained unclear [5, 18]. The findings from Prasad *et al*, coupled with the findings of hypergonadotrophic hypogonadism from the present study, makes zinc supplementation in sickle cell disease a potentially beneficial adjunct to routine folic acid and vitamin B12 supplementation for SCA patients in our setting. The potential impacts of the use of the afore-mentioned micronutrients were however not evaluated in this study as only two of the patients with sickle cell anaemia in this study were not taking any supplements. The effect of hydroxyurea was also not evaluated for the same reason.

The present study also explored the impacts of disease severity, nutritional status and socio-demographic characteristics of subjects on pubertal development. Severity of sickle cell disease is typically defined in terms of frequency of crises, hospital admission, blood transfusions and levels of markers of haemolysis. Logistic regression analysis showed a positive correlation between advanced age, high socioeconomic status of the parents, nutritional status and maternal menarcheal age and pubertal development, while frequency of crises and blood transfusion were negatively associated with puberty. However, only advanced age was statistically significant in both males and females.

Analyses in a previous study [13] suggest that growth status reflected the long-term manifestation of haemoglobin level, nutritional status, and other factors (e.g. maternal education). However, a study in Tanzania found these to be significant in males only [13]. It was suggested that improvement in standard of living via provision of basic amenities should be made affordable and available.

Interestingly, primary hypogonadism in SCA has been reversed with the use of hormonal replacement therapy. Morrison *et al* [19] documented reversal of hypogonadism in adolescent SCA subjects by testosterone replacement therapy without predisposing them to episodes of priapism. Timely identification and treatment of these disorders is therefore necessary, especially in resource poor settings where diagnosis of endocrinopathies in SCA is often delayed or altogether missed because of the greater clinical attention paid to the numerous acute complications associated with haemoglobinopathy.

Conclusion and Recommendation

The present study demonstrated that sickle cell anaemic patients have delayed onset and completion of puberty when compared to HbAA controls. Hormonal assays also revealed primary hypogonadism in patients with sickle cell anaemia. Screening for pubertal development and other endocrine complications should therefore be incorporated into the comprehensive care model for SCA for early detection of such impairments and prompt institution of appropriate interventions.

Conflict of Interest

None.

References

1. Rees DC, Williams TN, Gladwin MT. Sickle-cell disease. Lancet. 2010; 376:2018-2031.
2. Thomson AM, McHugh TA, Oron AP, Teply C, Lonberg N, Vilchis Tella VM, *et al*. Global, regional, and national prevalence and mortality burden of sickle cell disease, 2000–2021: A systematic analysis from the Global Burden of Disease Study 2021. Lancet Haematol. 2023; 10(8):e585-99.
3. Williams TN. Sickle Cell Disease in Sub-Saharan Africa. Hematol. Oncol. Clin. North Am. 2016; 30:343-358.
4. World Health Organization WHO. Sickle-cell anaemia: Report by the Secretariat [Internet]. [cited 2024 Dec 17]. Available from: https://iris.who.int/handle/10665/20890.
5. Smiley D, Dagogo-Jack S, Umpierrez G. Therapy Insight: Metabolic and endocrine disorders in sickle cell disease. Nat, Clin. Pract. Endocrinol. Metab. 2008; 4:102-109.
6. Al-Saqladi AWM, Cipolotti R, Fijnvandraat K, Brabin BJ. Growth and nutritional status of children with homozygous sickle cell disease. Ann. Trop. Paediatr. 2008; 28:165-189.
7. Thomas PW, Singhal A, Hemmings-Kelly M, Serjeant GR. Height and weight reference curves for homozygous sickle cell disease. Arch. Dis. Child. 2000; 82(3):204-208.
8. Zemel BS, Kawchak DA, Ohene-Frempong KO, Schall JI, Stallings VA. Effects of Delayed Pubertal Development, Nutritional Status, and Disease Severity on Longitudinal Patterns of Growth Failure in Children with Sickle Cell Disease. Pediatr Res. 2007; 61(5):607-613.
9. Abudu EK, Akanmu SA, Soriyan OO, Akinbami AA, Adediran A, Adeyemo TA, *et al*. Serum testosterone levels of HbSS (sickle cell disease) male subjects in Lagos, Nigeria. BMC Res. Notes. 2011; 4:1-5.
10. Abbiyesuku FM, Osotimehin BO. Anterior pituitary gland assessment in sickle cell anaemia patients with delayed menarche. Afr. J. Med. Med. Sci. 1999; 28(1-2):65-69.
11. Oyedeji G. Socio-economic and Cultural Background of Hospitalized Children in Ilesha. Niger. J. Paediatr. 1985; 12:111-117.
12. Modebe O. The effect of homozygous sickle cell disease on the age at menarche in Nigerian schoolgirls. Ann. Hum. Biol. 1987; 14(2):181-185.
13. Jacob T. Growth and pubertal development in children with sickle cell anaemia at Muhimbili National Hospital 2010. (Doctoral dissertation, Muhimbili University of Health and Allied Sciences.). Cited 2024 Dec 17. Available from: http://hdl.handle.net/123456789/53
14. Soliman AT, Elzalabany M, Amer M, Ansari BM. Growth and Pubertal Development in Transfusion-dependent Children and Adolescents with Thalassaemia Major and Sickle Cell Disease: A Comparative Study. J. Trop. Pediatr. 1999; 45(1):23-30.
15. Platt O, Rosenstock W, Espeland M. Influence of sickle haemoglobinopathies on growth and development. N. Engl. J. Med. 1984; 311:7-12.
16. Özen S, Ünal S, Erçetin N, Taşdelen B. Frequency and Risk Factors of Endocrine Complications in Turkish Children and Adolescents with Sickle Cell Anemia. Turk. J. Hematol. 2013; 30(1):25-31.
17. El-Hazmi MAF, Bahakim H, Al-Fawaz I. Endocrine functions in Sickle Cell Anaemia Patients. J. Trop. Pediatr. 1992; 38(6):307-313.
18. Prasad AS, Cossack ZT. Zinc supplementation and growth in sickle cell disease. Ann. Intern. Med. 1984; 100:367-371.
19. Morrison BF, Madden W, Clato-Day S, Gabay L. Testosterone Replacement Therapy in Adolescents with Sickle Cell Disease Reverses Hypogonadism Without Promoting Priapism: A Case Report. Urol. Case Rep. 2015; 3(6):179-180.