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Growth Patterns in Children with Sickle Cell Anemia during Puberty

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Abstract

Background—Previous studies of children with homozygous sickle cell anemia (SCA) show impaired growth and maturation. The correlation of this suboptimal growth with metabolic and hematological factors during puberty is poorly understood.

Procedure—We studied a group of pre-adolescent children with SCA (19 males, 14 females) and healthy controls (16 males, 15 females) matched for race, sex, body size, and pubertal development. Height, weight, body mass index (BMI), and body composition changes were longitudinally assessed over a 2-year period and compared between the groups and with Z scores based on US growth charts. These changes were correlated with hemoglobin concentration and with energy expenditure measured using indirect whole-room calorimetry.

Results—Children with SCA progressed through puberty slower than control children. While, after 2 years, pubertal males with SCA were shorter, their annual increases in weight were not different from controls. The mean fat free mass (FFM) increments were significantly less in males and females with SCA than in control children. In males with SCA, growth in height declined over time and was significantly slower than in matched controls ($p<0.05$).

Conclusion—Growth delays were present during puberty in children with SCA. Decreased growth velocity in children with SCA was independently associated with decreased hemoglobin concentration and increased total energy expenditure.

Keywords

growth; energy expenditure; body composition

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INTRODUCTION

Advances in the clinical care of children with sickle cell anemia (SCA), such as earlier diagnosis, penicillin prophylaxis, folate supplementation and hydroxyurea therapy have reduced morbidity and mortality related to this disease [1,2]. Suboptimal growth, however, remains a significant clinical problem. Compared to their healthy peers, studies suggest that children with SCA are smaller and have delayed pubertal development. Whether or not their ultimate adult weight and body mass index (BMI) remain lower is controversial; some studies have shown that young adults with sickle cell disease are smaller than their age-matched peers, [3-7] but the cohort study from Jamaica demonstrated normal adult height [8,9].

The importance of investigating the reasons for poor growth and delayed puberty and identifying possible modifiable factors that may promote more normal development in children with SCA has only recently been recognized. It has been reported that adequacy of dietary intake declines with age in children with SCA. However, changes in energy metabolism associated with SCA have not been fully studied. Further, there are controversial reports regarding association of hemoglobin levels with height and weight in females and males with SCA [7,10].

The objective of the present study was to systematically study the correlations between growth and hemoglobin and energy expenditure in children with SCA and developmentally matched healthy controls. We tested the hypothesis that growth rate in pubertal children with SCA is slower than in controls and is associated with hemoglobin concentration and total energy expenditure.

METHODS

Participants

A group of 33 African-American children with SCA were identified for participation in the study at the Pediatric Sickle Cell Clinic at Vanderbilt in Nashville, TN and at the MidSouth Sickle Cell Clinic in Memphis, TN from June 2001 to January 2006. The group screened and recruited for the study at the Clinical Center at Vanderbilt University Medical Center (CRC) included 19 males and 14 females, 10 to 13-years-old. Additionally, 31 African-American children from Nashville, who did not carry the sickle cell (HbS) gene or any other hemoglobinopathy were matched for sex, Tanner stage, and approximate height, weight, and fat mass to serve as a control for the study. The presence or absence of homozygous sickle cell disease (SCA) was confirmed through hemoglobin electrophoresis in all participants [11]. Patients with vaso-occlusive or pain crisis in the two months before screening, receiving chronic transfusion, on hydroxyurea therapy at baseline, or having apparent metabolic, skeletal, hepatic, or renal dysfunction, as well as pregnant females, were excluded from enrollment in the study. There were no subjects with disease characterized by stroke, multiple episodes of acute chest syndrome, or greater than three hospitalizations per year for pain due to the exclusion criteria of hydroxyurea or chronic transfusion. Self-reported complications occurring between the study visits were recorded. All children in the study were prescribed folic acid 1mg orally per day by their primary hematologist. Children and their parents or guardians received written information, verbal explanation about the nature and purpose of the study, and signed informed assent or consent according to the Declaration of Helsinki. The form was approved by both Vanderbilt University School of Medicine and Meharry Medical College for procedures to be performed at the CRC.

Procedures

Children were evaluated at baseline and annually for 2 years as part of a comprehensive study on energy balance that included annual measurement of total and resting energy expenditure, intake of energy and nutrients, and physical activity. Prior to participation in the study, subjects gave a medical history and underwent a complete physical examination. Children's Tanner pubertal staging was assessed on physical examination at baseline, at year 1, year 2 of the study using self-assessment questionnaire [12,13] used previously in our laboratory [14,15]. Hormone levels were measured at study entry and at each visit [12] and compared to normal ranges of hormone levels at puberty [16].

Anthropometrics and Body Composition

Body weight was measured to the nearest 0.05 kg with a monthly calibrated digital scale (Detecto-Medic, Detecto Scales, Inc, Northbrook, IL) with the participants wearing minimal clothing and no shoes. Height was measured using a wall-mounted stadiometer that was calibrated upon wall installation and recalibrated yearly (Perspective Enterprises, Portage, MI). Fat Mass, FFM and BMD were determined by dual energy x-ray absorptiometry (DXA, Lunar Prodigy, GE Medical Systems, Madison WI, children software, version 9.15) as previously described [17]. Our laboratory's intra-assay coefficient of variation for percent of FM using DXA is 0.79±0.49%.

Energy Expenditure

Resting and total energy expenditure were measured using whole-room indirect calorimetry described previously [18]. During the study, participants received a diet designed by a study dietitian and prepared at the CRC metabolic kitchen that contained 50±5% of the energy from carbohydrate, 30±3 % from fat, 15±3% from protein, and all required micronutrients. Participants spent 24 hours in the room calorimeter, in a strictly controlled environment (temperature and humidity), and followed a standardized protocol. The amount and intensity of physical activity performed was based on physical activity assessed in free living as described previously [15]. This approach minimized possible influence of physical activity and, at least in part, other environmental factors on outcome variables.

Resting energy expenditure (REE, kcal/min) was defined as the average energy expenditure (EE) during a 30-min period while the subject lay quietly in bed on the morning following an overnight sleep and 10 h of fasting as described previously [14,19]. *Total energy expenditure (TEE, kcal/kg/day)* was defined as the total energy per kilogram of body weight spent during an approximately 24 hour stay in the room calorimeter and extrapolated to 24 h (actual range was 22.5 - 23.5 hours).

Blood collection and analytical procedures

Hematological parameters that included whole blood hemoglobin concentration, packed cell volume, white blood cell count, reticulocyte count, ferritin, platelet count, red blood cells, and red blood cell folate were measured at Vanderbilt University Hospital Laboratory. Plasma albumin, thyroid-stimulating hormone, growth hormone, testosterone, estradiol, insulin, and leptin were measured at specialized Vanderbilt's Core Laboratories. All assays were performed using standard methodologies.

Statistical Analysis

Data are presented as mean ± standard deviation (SD). Continuous variables were compared using an unpaired Wilcoxon rank sum test between the SCA group and the control group. Since male and female children experience different growth patterns, they were compared separately. In addition, growth changes in height, weight, and BMI from baseline were

characterized using Z scores calculated based on the U.S. growth charts webbed by the Center for Disease Control (http://www.cdc.gov/nccdphp/dnpa/growthcharts/resources/sas.htm). Mixed effect models were used with disease status (SCA versus control), sex, hemoglobin concentration, total energy expenditure (per day per kilogram), and Tanner score as fixed effects and a random subject effect to analyze the endpoints. P values less than 0.05 were considered statistically significant and all tests were two-tailed. Analyses were performed using R-software version 2.6.2 (www.r-project.org) and SAS for Windows (Version 9.1.3, SAS, Cary, NC).

RESULTS

Participant characteristics at baseline

At the study entry, there were no significant differences in height, weight, BMI, FM, FFM, or Tanner staging between children with SCA and control children. Males with SCA were on average 0.9 years older and females with SCA were on average 1.7 years older than control children ($p< 0.05$); Table I). Males with SCA also had significantly lower bone mineral density (BMD) at study entry compared to control males (0.93 ± 0.05 g/cm^3 vs. 0.99 ± 0.06 g/cm^3, $p< 0.05$), females had BMD values that were not significantly different between females with SCA and controls. During the course of the study, 1 male and 3 females with SCA, and 1 control male and 1 control female dropped out of the study.

Hematological indicators, hormone levels, and energy expenditure

As expected, hematological parameters at baseline were significantly different between controls and children with SCA in both males and females (Table I). Data for some less important parameters are not shown. There were no statistically significant differences between control children and children with SCA in levels of thyroid hormone, growth hormone, estradiol (females only), testosterone (Table II, $p>0.05$), leptin, or insulin (data not shown). Children with SCA had higher REE compared to control children, but there was no significant difference in TEE spent at baseline or at years 1 and 2 ($P>0.05$).

Longitudinal growth patterns and body composition changes

The changes in height, weight, and BMI are presented in Table III. *Height:* For females with SCA height change was lower than in healthy controls at year 1, but similar in year 2. For males with SCA, changes in height from baseline to year 2 were lower than changes in healthy controls due to significantly greater height change among controls in year 2. Differences between the groups in changes of height Z score are presented in Figure 1. *Weight and BMI:* There were no significant differences in weight or BMI at baseline or in years 1 or 2 for either males or females. *Body composition:* There were no significant differences in FM and FFM between males and females with SCA and control children at baseline; however, the mean FFM increments after 2 years were significantly smaller in males and females with SCA than in control children (Table III). *Bone mineral density:* Changes in bone mineral density (BMD) were not different in both groups, although males with SCA had significantly lower (BMD) at baseline. *Pubertal development:* Males and females were matched for Tanner staging at baseline, but both control males and control females progressed through puberty more rapidly than those with SCA (Table IV).

Mixed effect regression analysis (Table V) showed that after adjusting for sex, Tanner stage, and disease status, the height and weight were positively associated with Hgb concentration, and weight and BMI negatively associated with TEE. The correlations between Hob concentration, weight, and height are shown in Figure 2.

DISCUSSION

The major finding of this study is that during puberty growth patterns are different in children with SCA than in non-SCA pubertal development matched controls and this difference is associated with Hgb concentration and total energy expenditure. Males with SCA had lower growth in height and lower BMD and entry and after two years than controls. Both males and females with SCA had lower FFM gain than controls. Pubertal attainment was slower in children with SCA than in healthy controls.

In our study, Hgb concentration was longitudinally associated with height and weight *Z* scores in both males and females (Figure 2). While children with SCA as a group did not had lower changes in weight and height Z scores than controls, the height and weight of children with SCA were found to be associated with Hgb concentration (Figure 2). Zemel at al. [7] found in their cohort of children that Hgb, hematocrit, and hemoglobin F concentration were associated with weight, height, and BMI scores in females but not in males. In contrast, Singhal et al. [20] reported that Hgb concentration was associated with height and weight in prepubertal Jamaican males, but not females. We previously showed that gender differences exist in the association of Hgb concentration with REE [14] and physical activity in free-living conditions [15]. Since Hgb concentration and REE were highly correlated (0.7) we used less correlated (0.3) TEE as a factor in the final models for the longitudinal mixed effects analysis predicting changes in growth status over time and found increased TEE to be an independent risk factor for poor growth. We feel that TEE is an important variable for sickle cell studies because it includes REE, as well as physical activity, and it is easier to use in calculating energy balance (energy intake minus total energy expenditure). We found that although changes in weight and BMI were not different between the groups, the BMI and weight of individuals were associated with their TEE.

These findings answer some questions raised by the results from the Stroke Prevention Trial [21] which suggested that growth failure is not inherent to the genetic disease of SCA. That study showed that children with SCA who were chronically transfused to maintain a hematocrit greater than 30% had significant improvement in height, weight, and body mass index (BMI) Z scores [22], such that after a mean of 2 years of chronic transfusion therapy, they were of comparable size to their peers without SCA. These findings raised the question as to whether impaired growth is purely a function of anemia, or if it is related to other aspects of the chronic disease [23,24]. Our study confirms that energy expenditure, in addition to hematological status, are factors affecting growth in children with SCA.

We compared children with SCA to race, gender, body size, and stage of puberty matched healthy control children independent of age. Despite that all children with SCA and majority of controls (90%) were at Tanner 2 stage at baseline, the control children progressed through puberty stages faster than the children with SCA. After two years of the study, 47% of control males and 86% control females progressed to Tanner 4 stage. At that time the majority of males (94%) and females (64%) with SCA were at Tanner 3 stage and only 6% of males and 36% of females with SCA progressing to Tanner 4 stage of development..

Other indices of pubertal development such as linear growth is steady in childhood, but increases from 5.5 cm/year in pre-pubertal children to a peak velocity of 8.3 cm/year in females and 9.5cm/year for males during puberty [25]. Therefore, one would expect children with SCA to have continued pubertal height velocity and possibly achieve normal adult heights. The differences in height velocity between children with SCA and controls are well illustrated in Figure 1.

Poor increase in BMD may be due to hormonal differences between control males, who were progressing through puberty over the 2-year study period, and SCA males who

remained in relatively early pubertal stages despite the passage of 2 years. While hormone levels were not statistically different due to a broad range in controls and males with SCA, the mean levels were higher in the control group. Another factor in BMD that has been investigated in other studies is calcium and vitamin D intake [26]. Calcium intake is often low in African Americans because of lactose intolerance and cultural dietary habits [27], as well as the poor calcium intake of this age-group in general [28]. Lal et al [29] found that low BMD in children with SCA was significantly associated with vitamin D status. In our study, vitamin D intake at baseline was lower in children with SCA than in controls (21.3 ± 16.2 vs. 34.3 ± 5.5 μmol/L; $p<0.05$). Because puberty is a critical time to increase BMD, it is encouraging that children with SCA have prolonged puberty and thus more time to intervene and improve their BMD and possibly decrease their risk for bone fracture as suggested by Buison et al.[30]. These authors also found lower whole body mineral content in SCA males than females with SCA also observed in our study. Further analysis of associations between BMD and other factors (i.e., Hgb, TEE) were limited by a relatively small cohort size that did not allow calculating population-specific BMD Z scores.

We followed our cohort for two consecutive years after baseline measurements. A longer follow-up period would very likely provide more comprehensive results. However, we documented important trends in growth patterns and their association with the hematological status and elements of energy balance. In this study, we did not evaluate the effects of hydroxyurea and long-term transfusion therapy on growth status in children with SCA. The benefits of these treatments have been reported in other studies [7,22,31,32].

Future intervention studies should assess potential benefits of both of these treatments and other medical strategies aimed to improve growth and development of children with SCA during puberty. Options include supplementation with protein for which requirements in SCA are unknown, and supplementation with micronutrients such as zinc, calcium and/or vitamin D [10,33]. The impact of increased requirements for energy, protein, and micronutrients in SCA combined with effects of possible endocrine abnormalities on pubertal growth in SCA needs to be further investigated.

Our study indicates that during puberty, children with SCA have a slower rate and different growth pattern than non-SCA controls, allowing a longer interval for interventions to improve height, weight, and BMD. Growth velocity in children with SCA is positively associated with hemoglobin concentration and negatively associated with total energy expenditure.

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Abbreviations

SCA	sickle cell anemia
BMI	body mass index

FFM	fat free mass
Hgb	hemoglobin
REE	resting energy expenditure
TEE	total energy expenditure

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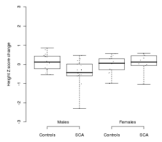

Figure 1.

Change from baseline in height Z score for boys and girls with SCA controls after 2 consecutive follow-up years. The figures illustrate individual Z score change (points), median (middle thick line), and a range between 1 and 3 quartiles (box). Lower and upper bars illustrate 1.5 interquartile range distance.

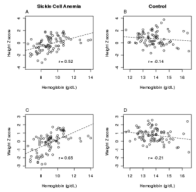

Figure 2.

Spearman-rho (r) correlations between hemoglobin concentration (g/dL) and height Z score (A and B) and weight Z score (C and D) in children with sickle cell anemia (SCA) (A and C) and matched healthy controls (B and D) measured at baseline and after 1 and 2 years.

TABLE I

Baseline characteristics of study participants

	Males		Females	
	Controls (*n* =16)	**SCA (*n* =19)**	**Controls (*n* =15)**	**SCA (*n* =14)**
Age (*years*)	10.43±0.93	11.29±1.21 *	9.98±0.95	11.70±1.62 *
Weight (*kg*)	36.36±5.65	37.11±7.60	41.27±8.29	39.33±9.37
Height (*cm*)	140.80±7.68	145.03±7.31	145.33±8.19	147.12±12.88
Body mass index *(kg/m^2)*	18.28±2.05	17.55±2.72	19.50±3.63	17.93±2.31
Fat-free mass *(kg)*	28.59±4.00	28.66±4.35	29.23±3.22	28.82±6.27
Body fat (*%*)	16.94±5.92	19.63±7.63	23.97±10.61	21.21±7.74
Bone mineral density *(g/cm3)*	0.99±0.06	0.93±0.05 *	0.99±0.066	0.96±0.09
Hemoglobin (*g/dL*)	13.56±1.21	8.93±1.62	13.82±1.32	9.14±1.33*

Values are expressed as means ± standard deviation (SD)

* significantly different from controls using Wilcoxon test ($p<0.05$).

TABLE II

Hormones level and energy expenditure in study participants

	Males		Females	
	Controls (*n* =16)	**SCA (*n* =19)**	**Controls (*n* =14)**	**SCA (*n* =14)**
Thyroid hormone (*mcU/ml*)	2.37±1.25	2.32±1.08	1.91±1.23	2.06±1.50
Growth hormone (*ng/ml*)	0.43±0.41	0.52±0.63	1.40±2.51	1.21±0.93
Estradiol (pg/ml)			27.5±15.2	35.6±44.1
Year 1			46.25±39.10	59.0±52.2
Year 2			82.08±36.95	48.0±53.3
Testosterone (ng/ml)	1.06±2.06	0.48±1.10	0.81±0.58	0.60±0.35
Year 1	1.63±2.31	0.46±0.71	0.54±0.31	0.40±0.23
Year 2	2.60±2.86	1.50±1.90	0.43±0.25	0.23±0.07 *
REE (*kcal/kg FFM/day*)	45.92±2.45	57.03±5.94 *	44.87±5.39	53.45±5.87 *
Year 1	43.95±3.94	55.62±4.25*	43.36±3.50	52.35±7.12
Year 2	41.89±3.86	51.84±5.59*	40.49±5.02	49.04±4.17*
TEE (*kcal/kg BW /day*)	47.41±5.77	50.49±4.66	45.86±4.15	45.94±6.39
Year 1	47.83±6.28	47.05±5.87	43.64±5.92	42.85±8.12
Year 2	45.85±7.60	44.22±4.58	39.07±4.80	38.04±6.45

REE – resting energy expenditure (kcal/kg fat free mass (FFM)/day); TEE- total energy expenditure (kcal/kg body weight (BW) per day); values are expressed as means ± SD

* significantly different from controls using Wilcoxon test ($p<0.05$).

Table III

Measures of growth status and body composition

	Males		Females	
	Controls (*n* =16)	**SCA (*n* =19)**	**Controls (*n* =15)**	**SCA (*n* =14)**
Height (cm)	145.80±7.68	145.03±7.31	145.33±8.19	147.12±12.88
Year 1 – change from baseline (%)	4.04±1.96	3.20±2.86	5.18±2.17	3.50±1.74 *
Year 2 – change from baseline (%)	8.86±2.68	6.46±3.67*	8.62±2.76	6.65±3.91
Weight (kg)	36.36±5.65	37.11±7.60	41.27±8.29	39.33±9.37
Year 1 – change from baseline (%)	14.56±7.13	13.33±7.19	16.81±6.90	14.37±5.32
Year 2 – change from baseline (%)	28.81±9.28	26.99±11.34	33.22±9.53	27.28±11.34
Body Mass Index at baseline (kg/m^2)	18.28±2.05	17.55±2.72	19.50±3.63	17.93±2.31
Year 1 – change from baseline (%)	5.83±5.48	6.52±7.20	5.64±6.28	6.758±4.252
Year 2 – change from baseline (%)	8.75±7.69	12.10±9.08	12.97±7.97	12.10±11.05
FFM at baseline (kg)	28.65±3.85	28.66±4.35	29.23±3.22	28.82±6.27
Year 1 – change from baseline (%)	13.4±11.1	9.6±6.1	15.4±7.5	9.8±5.0*
Year 2 – change from baseline (%)	30.5±14.7	20.3±9.1*	27.9±8.97	19.3±10.4*
Bone mineral density at baseline (g/cm^3)	0.99±0.06	0.93±0.05 *	0.99±0.07	0.96±0.09
Year 1 – change from baseline (%)	1.7±3.2	2.2±2.8	4.0±4.8	3.1±3.9
Year 2 – change from baseline (%)	5.0±5.1	3.6±3.8	6.8±6.2	6.3±3.4

Values are expressed as means ± SD (range)

* significantly different from controls using Wilcoxon test ($p<0.05$); changes from baseline were summarized by means ± SD of the individual changes.

Table IV

Number of children at each Tanner stage during the study

		Males		Females	
		Controls (*n* =16)	**SCA (*n* =19)**	**Controls (*n* =15)**	**SCA (*n* =14)**
Baseline -	Tanner 2	16 (100%)	19 (100%)	13 (87%)	13 (93%)
	Tanner 3	0	0	2 (13%)	1 (7%)
	Tanner 4	0	0	0	0
Year 1 -	Tanner 2	3 (20%)	12 (67%)	1 (7%)	6 (55%)
	Tanner 3	12 (80%)	6 (33%)	14 (93%)	5 (45%)
	Tanner 4	0	0	0	0
Year 2 -	Tanner 2	0	0	0	0
	Tanner 3	8 (53%)	17 (94%)	2 (14%)	7 (64%)
	Tanner 4	7 (47%)	1 (6%)	12 (86%)	4 (36%)

TABLE V

Prediction of growth status during the study using multiple regression

	Coefficient	p-value	lower 95% C.I.	upper 95% C.I.
Height (cm)				
Disease status (0-control, 1 – sickle cell anemia)	4.45	0.10	−0.92	9.81
Sex (0- female, 1 male)	0.34	0.85	−3.40	4.09
Hemoglobin (g/dL)	0.23	0.59	−0.61	1.07
Total energy expenditure (kcal/kg/day)	−0.37	<0.001	−0.53	−0.20
Tanner stage	5.81	<0.001	4.78	6.83
Weight (kg)				
Disease status (0-control, 1 – sickle cell anemia)	2.04	0.42	−2.94	7.02
Sex (0- female, 1 male)	0.92	0.60	−2.54	4.37
Hemoglobin (g/dL)	0.31	0.43	−0.47	1.10
TEE (kcal/kg/day)	−0.46	<0.001	−0.62	−0.31
Tanner stage	5.55	<0.001	4.59	6.50
BMI (kg/m^2)				
Disease status (0-control, 1 – sickle cell anemia)	−0.58	0.54	−2.46	1.30
Sex (0- female, 1 male)	0.26	0.71	−1.13	1.65
Hemoglobin (g/dL)	0.03	0.83	−0.25	0.31
TEE (kcal/kg/day)	−0.11	<0.001	−0.16	−0.05
Tanner stage	0.93	<0.001	0.61	1.26

Models for the longitudinal mixed effects analysis predicting changes in growth over time; Tanner stage (1 to 4) were assessed at each visit and entered into the models as variables; hemoglobin (Hgb) concentration and total energy expenditure (TEE) were measured at each visit (baseline, year 1, and year 2).