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Original Article

Paediatrics Section

Sexual Maturity in Adolescents Suffering from Sickle Cell Disease: A Cross-sectional Study

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ABSTRACT

Introduction: Sickle Cell Disease (SCD) is an inherited chronic haemolytic anaemia. The diseased person suffers from various complications such as anaemia, frequent infection, fever, hand-foot syndrome, stroke, etc. Puberty changes includes the appearance of the secondary sexual characteristics, increase in height, change in body composition and development of reproductive capacity.

Aim: To study the sexual maturity and effect of multiple blood transfusions in adolescents suffering from SCD.

Materials and Methods: It was a cross-sectional study conducted on 35 adolescents of age group 11 to 15 years, suffering from SCD. Study was conducted over a period of six months from March 2018 to September 2018 at Department of Paediatrics, Government Medical College, Surat, Gujarat, India. The SCD was diagnosed by Haemoglobin (Hb) electrophoresis. Weight and height of all the participants were measured. For assessing the sexual maturity, Tanners staging was used, also known as Sexual Maturity Rating (SMR). Unpaired t-test was done for data analysis.

Results: The mean age of the patients was 13.03±1.7 years. There were 25 males and 10 females. The mean age of male patients between Tanner stage 2 (14.63±0.52 years) and Tanner stage 3 (14.75±0.5 years) was significantly higher than the Indian data for males (11.3 and 12.8 years, respectively). The mean age of female patients between Tanner stage 2 (13.5±2.12 years) and Tanner stage 3 (14.33±1.16 years) was higher than the Indian reference data for girls (10.2 and 11.6 years respectively).

Conclusion: This study concluded that adolescents with SCD were significantly shorter in height and weight than the standard reference population. Sexual maturity is delayed in adolescents with sickle cell anaemia.

Keywords: Blood transfusion, Body weight, Growth, Haemolytic anaemia, Menarche

INTRODUCTION

Sickle cell anaemia is an inherited chronic haemolytic anaemia. The clinical manifestations of sickle cell anaemia results from deforming red blood cells (HbS). Strasser BJ explained that the haemoglobin of a patient with sickle cell anaemia (HbS) differed in electrophoretic mobility [1]. Ingram VM described the replacement of valine with glutamine by normal HbS-producing haemoglobin [2]. The homozygous state is the most common form of sickle cell anaemia [3].

About 50% of the world population of SCD cases are in India [4]. Estimates indicate that the sickle cell trait is predominant among the tribal population of Central India [5]. In India, it is mainly seen among tribal populations in Western, Central, Eastern and parts of Southern India and some non tribal communities [6]. A high prevalence of the sickle gene has been demonstrated in several tribal communities in Gujarat, India [7].

Red blood cells supply oxygen and nutrients that are essential for the growth. Deficiency of blood cells can decline growth in children thus, delay puberty in teenagers. The rate of growth is lower than normal in SCD patients, and the puberty growth spurt is delayed by 1-2 years. Delay also occur in skeletal maturation and onset of puberty, and female patients achieve menarche 1-2 years later than their peers [8].

Puberty is the biological transition from childhood to adulthood. Puberty changes includes the appearance of secondary sexual characteristics, increase in height, change in body composition and development of reproductive capacity. The progression of the development of secondary sexual characteristics can be described using the Sexual Maturity Rating scale (SMR) (ranging from 1, preadolescence, to 5, sexual maturity) or Tanner stages [8,9].

Singhal A et al., in West Indies in 1994, Aina OF et al., in Nigeria in 2010 and Rhodes M et al., in Nashville in 2009 showed that the control children progressed through puberty stages faster than the children with SCA [10-12]. Taking into consideration the above scenario the present study was initiated to find the effect of SCD on sexual maturity in adolescents.

MATERIALS AND METHODS

The present cross-sectional study was conducted at Department of Pediatrics, Government Medical College, Surat, Gujarat, India, from March 2018 to September 2018. The SCD was diagnosed by High-Performance Liquid Chromatography (HPLC). Ethical approval was taken with letter number No.Mcs/Stu/Ethics/Approval/6252/18 Date:-16/03/18 from the Institutional Ethical Committee. Total 35 patients were selected who visited the Out Patient Department (OPD) with SCD from March 2018 to September 2018.

Inclusion criteria: Adolescents of age group 11 to 15 years suffering from SCD were included.

Exclusion criteria: Patients with vaso-occlusive or pain crisis having apparent metabolic, skeletal, hepatic, or renal dysfunction and those didn't give consent for the study were excluded.

Methodology

The purpose and objectives of the study were explained to parents and guardians of children suffering from SCD. After taking appropriate written consent, medical history was taken, and a thorough clinical examination was done on each child with special emphasis on Tanners staging [8]. Age was calculated from the date of birth mentioned by the parents. Weight was recorded on a weighing machine with maximum capacity of 120 kg and the sensitivity of the weighing scale was up to 100 grams. Height was recorded using a stadiometer in standing position with feet closed, head and the body touching the stadiometer. Parents were inquired about number of crisis, hospitalisation, numbers of blood

transfusions, about family screening and sibling screening as well. Data of sickle cell adolescents were compared to standard normal values in adolescents of the same age group [13].

STATISTICAL ANALYSIS

The data entry was done using Microsoft Excel 2016 and data analysis was done using Microsoft Excel 2016, International Business Machine Statistical Package for the Social Sciences (IBM SPSS) statistical software 20.0 and Epi info software. Unpaired t-test was also used for analysis.

RESULTS

Total of 35 patients were included with mean age of 13.03±1.7 years, having minimum age 11 years and maximum age being 15 years, who visited the OPD with SCD from March 2018 to September 2018. More than one third of the patients were 15-year-old (34.3%). More than two-third of the patients (71.4%) were males with male to female ratio of 2.5:1 [Table/Fig-1].

Age (years)	Gender	
	Male (n) (%)	Female (n) (%)
11	7 (28)	4 (40)
12	4 (16)	1 (10)
13	2 (8)	1 (10)
14	4 (16)	0
15	8 (32)	4 (40)
Total	25 (100)	10 (100)

[Table/Fig-1]: Age and Gender wise distribution of all patients.

Males had significantly lower mean value of weight compared to reference weight among Indian boys of respective age group (p<0.05). The 11, 12 and 14-year-old males had significantly lower mean value of height compared to reference height among Indian boys of respective age group (p<0.05) [Table/Fig-2].

Age (Years)	No. of patients (n)	Weight (kg) (mean±SD)	Reference weight (kg)	p-value (Student's t-test)
11	7	30.0±2.8	35±8.9	0.003
12	4	30.3±2.4	40±10.0	0.004
13	2	35.3±0.3	43±11.3	0.017
14	4	35.2±1.8	47±12.1	0.001
15	8	40.4±1.9	53±12.1	0.015
Age (years)	**No. of patients (n)**	**Height (cm) (mean±SD)**	**Reference height (cm)**	**p-value (Student's t-test)**
11	7	135±3.5	143±7.6	0.001
12	4	138.8±2.1	146±8.1	0.002
13	2	148±1.4	155±9.0	0.090
14	4	148±2.9	160±9.0	0.004
15	8	162.6±4.8	165±7.9	0.192

[Table/Fig-2]: Age wise comparison of mean weight and height among boys with Indian reference boys.
(p-value <0.05 significant)

In present study, 11 to 15-year-old females had significantly lower mean value of weight compared to reference weight among Indian girls of respective age group (p<0.05). However, 12 and 13-year-old females had lower mean weight compared to the Indian reference data. However, 15-year-old females had non significantly higher mean value of height compared to reference height among Indian girls of this age (p>0.05). Also, 12 and 13-year-old females had lower height compared to Indian reference girls, but p-value could not be calculated because of zero Standard Deviation (SD) [Table/Fig-3].

Age (Years)	No. of patients (n)	Weight (kg) (mean±SD)	Reference weight (kg)	p-value (Student's t-test)
11	4	25.4±2.1	34±8.5	0.004
12	1	28.6±0.0	40±9.0	---
13	1	37.3±0.0	43±9.4	---
15	4	36.1±7.7	48±9.6	0.049
Age (years)	**No. of patients (n)**	**Height (cm) (mean±SD)**	**Reference height (cm)**	**p-value (Student's t-test)**
11	4	129.3±8.8	143±7.9	0.053
12	1	134.0±0.0	146±7.0	----
13	1	152.0±0.0	152±6.9	----
15	4	158.5±9.3	156±6.4	0.258

[Table/Fig-3]: Age wise comparison of mean weight among girls with Indian reference girls.
(p-value <0.05 significant)

The majority of the patients (17, 48.6%) belonged to Tanner staging 1, followed by Tanner staging 2 (10, 28.6%). Among male patients, more than half of the patients (13, 52%) belonged to Tanner stage 1. However, among female patients, majority (4, 40%) belonged to Tanner stage 1 [Table/Fig-4].

Tanner staging (SMR)	Gender		Total (%) (N=35)
	Male (n) (%)	Female (n) (%)	
1	13 (52)	4 (40)	17 (48.6)
2	8 (32)	2 (20)	10 (28.6)
3	4 (16)	3 (30)	7 (20)
4	0	1 (10)	1 (2.8)
Total	25 (100)	10 (100)	35 (100)

[Table/Fig-4]: Distribution of patients based on gender and tanners staging.

Mean age of the male SCD patients in different Tanner staging were compared with Indian reference age in different Tanner staging in both genders. Mean age of male SCD patients in present study among Tanner stage 2 (14.63±0.52 years) and Tanner stage 3 (14.75±0.5 years) was significantly higher compared to Indian reference boys (11.3 and 12.8 years, respectively) (p<0.05). Mean age of female SCD patients in present study among Tanner stage 2 (13.5±2.12 years) and Tanner stage 3 (14.33±1.16 years) was higher comparing to Indian reference girls (10.2 and 11.6 years, respectively) (non significant, p>0.05) [Table/Fig-5].

Gender	Tanner staging (SMR)	No. of patients (n)	Age (Years) (Mean±SD)	Reference age (years)	p-value (Student's t-test)
Male	1	13	11.62±0.77	10.4±1.0	0.002
	2	8	14.63±0.52	11.3±1.2	<0.001
	3	4	14.75±0.50	12.8±1.2	0.004
Female	1	4	11.0±0.0	10.5±1.0	0.356
	2	2	13.5±2.12	10.2±1.1	0.272
	3	3	14.33±1.16	11.6±1.3	0.055
	4	1	15.0±0.0	13.5±1.2	--

[Table/Fig-5]: Comparison of patients' age with Indian reference age in different Tanner staging.
(p-value <0.05 significant)

Most of the patients (82.9%) required blood transfusions. Among them, 48.3% of patients belonged to Tanner stage 1, 34.5% to stage 2, 13.8% to stage 3 and the remaining 3.4% to Tanner stage 4 [Table/Fig-6].

Tanner staging (SMR)	Blood transfusion	
	Not required (%)	Required (%)
1	3 (50)	14 (48.3)
2	0	10 (34.5)
3	3 (50)	4 (13.8)
4	0	1 (3.4)
Total	6 (100)	29 (100)

[Table/Fig-6]: Distribution of patients based on Tanner staging and requirement of blood transfusion.

DISCUSSION

The SCD is a condition present in Indian population and usually considered clinically benign. It is generally believed that SCD has an adverse effect upon the physical growth and development, and however, published data on this aspect from India is meager [14]. Present study deals with the growth and development of SCD subjects.

In the present study, the mean age of the patients was 13.03±1.7 years, with more than one third of patients were 15-year-old. More than two thirds of patients were men with a 2.5:1 male:female ratio. In the study by Aina OF et al., the minimum age of the patients was 10 years and the maximum age 19 years [11]. A total of 136 adolescents with Pain Catastrophising Scale (PCS) and of equal gender distribution were studied, with a mean age of 14.3±2.6 years. In the study by Cepeda ML et al., study subjects ranged in age from 8.3 to 19.5 years and 63% (19/30) of the couples were male and 37% (11/30) were female [15].

The mean age of male patients with SCD in the present study between Tanner stage 2 and Tanner stage 3 was significantly higher than the Indian reference children. The mean age of SCD patients in the present study between Tanner stages 2 and 3 was higher than the Indian reference girls.

In the study by Serjeant GR et al., the mean age at menarche was 13.0 years in AA controls, 13.5 years in SC disease and 15.4 years in SS disease [16]. It was concluded that the mean age of menarche is delayed by 0.5 years in HF disease and by 2.4 years in SS disease.

In the present study, children aged 11 to 15 years with sickle cell anaemia had a mean weight value significantly lower than the baseline weight in Indian children in the respective age group ($p<0.05$). Among the girls with sickle cell anaemia, they had a mean weight value lower than the baseline weight in the Indian girls in the respective age group (significant in the age group 11 and 15 years).

Among 11, 12 and 14-year-old males had significantly lower mean value of height compared to reference height among Indian boy of the respective age group. Among 11, 12, and 13-year-old girls with sickle cell anaemia, the mean height value was not significantly lower than the baseline height in Indian girls of the respective age group.

In the study by Zemel BS et al., it was observed that from admission to the last visit, 84% of children declined in one or more of the growth indicators [17]. Kumar S and Mukherjee MB, Gangakhedkar RR found out that children with SCD were of less weight and shorter height than the comparable normal controls [18,19].

Rhodes M et al., found that children with PCS progressed more slowly during puberty than control children [12]. Although males with ACS were shorter after two years, their annual weight gains were no different from controls. Mean gains in lean body mass were significantly lower in men and women with ACS than in control children. In males with SCA, growth in height was significantly slower than matched controls. In the study Cepeda M et al., the control subjects weighed just over 12 kg more than the study subjects for each pair [15]. The control subjects were also significantly taller, averaging just over 8 cms per pair. Mukherjee MB and Gangakhedkar RR found that the delay in growth starts in early childhood but becomes more apparent during adolescence when the growth spurt of normal children separates them from the patients with SCD [19].

In the study by Rhodes M et al., all children with PCS and most of the controls (90%) were Tanner stage 2 at baseline. After two years of study, 47% of control males and 86% of control females progressed to Tanner stage 4. At that time, only 6% of males and 36% of females with SCA had progressed to developmental stage 4 by Tanner [12].

The study by Singhal A et al., concluded that early puberty changes (Tanner stage 2) appeared later in subjects with sickle cell anaemia (SS) than in hematological normal (AA) controls for all 42 couples. Age at menarche in girls with SS disease was significantly later than in girls with heart failure disease and in those with a normal haemoglobin AA genotype. Early puberty changes (Tanner stage 2) appeared later in SS subjects, men at 12.8±1.6 years and women at 12.0±1.8 years compared to AA controls (men: 11, 1±1.2 years; women: 10.1±1.2 years) [10]. The study by Aina OF et al., concluded that, for both men and women, subjects lagged significantly behind controls in several areas of sexual maturation [11].

In the present study, most patients with sickle cell anaemia (82.9%) required blood transfusions. Among them, the majority of patients belonged to Tanner stage 1. The study by Zemel BS et al., found that transfusion therapy has no effect on growth over time, but children had less severe bone age retardation who received long term transfusion therapy [17]. They concluded that the growth state reflects the long term effects of severe anaemia, malnutrition and other factors rather than the acute effects of SCD-related complications leading to long term transfusion therapy.

Limitation(s)

In this study, did not evaluate the effects of hydroxyurea and long term transfusion therapy on growth status in children with SCA and did not follow patients after baseline measurement.

CONCLUSION(S)

Impaired growth is a known complication of SCD. This study revealed that adolescents with SCD were significantly shorter in height and weight than the standard reference population. Sexual maturity is delayed in adolescents with sickle cell anaemia.

Puberty is a time of great change for every child and for their parents as well. If delayed puberty is explained early, it can reduce many unexpected complications. Genetic counselling is needed to reduce the prevalence of PCS and raise awareness of the disease. This deadly disease can be prevented by taking measures such as premarital screening, genetic counselling, and prenatal diagnosis.

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