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RESEARCH ARTICLE

TRAVERSING THROUGH THE PATH OF PUBERTY: A CROSS-SECTIONAL STUDY ON SEXUAL MATURATION AMONG SICKLE CELL DISEASE PATIENTS

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ABSTRACT

Introduction: Sickle cell disease (SCD) is a condition where red blood cells take on a sickle shape due to abnormal hemoglobin production. This affects various bodily systems and can lead to growth and developmental delays, including delays in reaching puberty. There is a scarcity of research regarding the sexual development of individuals with sickle cell disease (SCD) in India. **Aim & Objectives**: The current study was conducted with an aim to investigate the sexual maturation process in individuals with sickle cell disease (SCD). The objective of study is to examine the impact of sickle cell disease on the development of secondary sexual characters among adolescents. **Methods**: A total of 45 SCD patients aged 10-16 years were selected from a pediatric department in India. The diagnosis of Sickle Cell Disease was confirmed using High-Performance Liquid Chromatography. Clinical examinations included Tanner staging, weight, and height measurements, compared to reference values. The statistical analysis was performed using SPSS Version 24.0. **Results**: Patients with sickle cell disease (SCD) showed significant differences in growth compared to standard values, particularly in terms of weight and height across various age categories. Sexual maturation, as determined by Tanner staging, exhibited a slower advancement in boys at all stages when compared to the standard ages for Indian individuals. Female patients displayed less consistent patterns, with significant differences observed in certain age groups. **Conclusion**: The study highlights the occurrence of delayed sexual maturation in Indian patients with sickle cell disease (SCD), particularly in boys. This emphasizes the necessity for customized treatments to specifically target these disparities. Additional investigation is necessary to clarify the intricate relationships between the severity of the disease, the treatment, and the onset of puberty in individuals with Sickle Cell Disease (SCD). **Final Message**: It is essential to comprehend the process of sexual maturation in individuals with sickle cell disease (SCD) in order to enhance clinical care and achieve better results. Customized interventions targeting growth disparities and delayed sexual maturation are crucial for improving the quality of life for individuals with SCD in India.

INTRODUCTION

Sickle cell anemia, also known as Herrick's anemia, is distinguished from other hemoglobinopathies by the formation of sickle-shaped red blood cells as a result of anomalous hemoglobin synthesis. Due to their rigidity, adhesion and propensity for aggregation; these cells obstruct blood vessels and induce organ injury, infections, and pain. Multiple physiological systems are impacted by the disease, which causes growth and development to be slowed and puberty to be delayed.[1] It manifests in homozygous individuals as an autosomal recessive genetic disorder, whereas heterozygotes only exhibit sickling without disease. Valine is introduced in place of glutamic acid at position six in the beta globin chain of hemoglobin due to a genetic single base pair mutation of thymine for adenine. Notwithstanding the physiological alterations it elicits sickle shape. Thus, sickle cell anemia confers a degree of resistance against malaria.[2] India is home to approximately fifty percent of all sickle cell disease cases worldwide.[3]The prevalence of the sickle cell trait among the tribal population of Central India is estimated to be high.[4] It is predominantly observed in tribal communities residing in Western, Central, Eastern, and portions of Southern India, as

well as certain non-tribal communities.[5] A comprehensive compilation of the prevalence of sickle cell disease, derived from a multitude of studies and publications, was presented in the Atlas on Haemoglobinopathies, which was released in February 2022 by the Indian Council of Medical Research, National Institute of Immunohaematology.[6] Sickle cell disease (SCD) patients experience a postponement of adolescent puberty due to cellular development being impeded by an inadequate supply of red blood cells. The growth and advent of puberty in these patients are generally delayed by one to two years, in addition to the maturation of the skeleton and the initiation of menstruation. Puberty regulates the transition from infancy to adulthood, which is characterized by the development of reproductive capacity and secondary sexual characteristics. Frequently, the Sexual Maturity Rating scale or Tanner stages, which span pre-adolescence (SMR 1) to sexual maturity (SMR 5), is employed to evaluate this development.[7]Despite the existence of research on physical maturation, information regarding the sexual maturation of Indian subjects is scarce. Therefore, the current study was conducted with an aim to investigate the sexual maturation process in individuals with sickle cell disease (SCD). The objective of study is to examine the impact of sickle cell disease on the development of secondary sexual characters among adolescents.

METHODOLOGY

This cross-sectional study was carried out at the Department of Pediatrics, Vedanta Institute of Medical Science, Vedantaa Hospital and Research Centre, India, between January 2024 and June 2024. The diagnosis of Sickle Cell Disease (SCD) was confirmed using High-Performance Liquid Chromatography (HPLC). After Obtaining ethical approval from the Institutional Ethical Committee. A total of 45 patients were chosen from those who sought treatment at the Out Patient Department (OPD) for Sickle Cell Disease (SCD) between January 2024 and June 2024. Adolescents boys from age 11to 16years and adolescent girls from age 10 to 15 years who have sickle cell disease (SCD) were included in the study. Exclusion criteria: Patients with vaso-occlusive or pain crisis accompanied by evident metabolic, skeletal, hepatic, or renal dysfunction, as well as those who did not provide consent for the study, were excluded.

The study's purpose and objectives were clearly communicated to parents and guardians of children afflicted with SCD. Upon obtaining the necessary written consent, a thorough medical history was obtained. A comprehensive clinical examination was conducted on each child, with particular focus on Tanner's staging. The age was determined based on the parents' provided date of birth. The weight was measured using a weighing machine that had a maximum capacity of 120 kg and a sensitivity of 100 grams. The height measurement was obtained by using a stadiometer while the individual was standing with their feet together and their head and body in contact with the stadiometer. Parents were surveyed regarding the frequency of crises, hospitalizations, blood transfusions, family and sibling screenings. The data of adolescents with sickle cell disease were compared to the standard normal values of adolescents in the same age group. The mean ± standard deviation (SD) was used to present continuous variables, while categorical variables were presented as n (%). The distributions of categorical variables were evaluated using Fisher's exact or Pearson's Chi-Square tests, with a significance level of $p < 0.05$. SPSS Version 24.0 streamlined the process of analyzing data.

RESULTS AND DISCUSSION

Within sample of 45 patients chosen from those who sought treatment at Out Patient Department (OPD) for Sickle Cell Disease (SCD). Adolescents boys from age 11 to 16years and adolescent girls from age 10 to 15years who have sickle cell disease (SCD), As shown in figure 1, 0%, 28.10%, 15.7%, 9.35%, 15.6%, 31.25% and 0% are male study participants in 10y, 11y, 12y, 13y, 14y, 15y and 16y respectively. While 0%, 38.6%, 7.6%, 7.6%, 7.6%, 38.6% and 0% in 10y,11y,12y,13y,14y, 15y and 16y respectively.

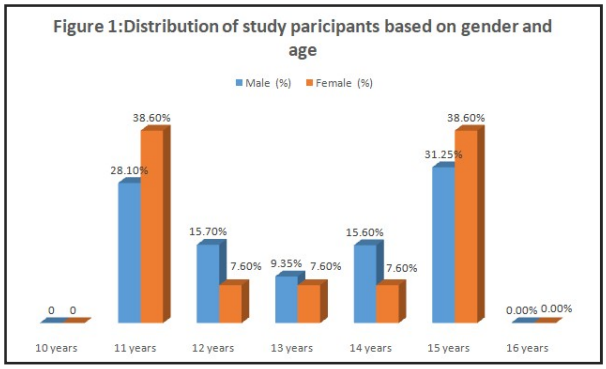

Figure 1.Distribution of study participants based on gender and age

Table 1 displays weight and height measurements among male participants at various age of 11y, 12y, 13y, 14y and 15y by comparing them to reference values. Thus, statistical significance is seen all weight and height measurements with for height at 13y and 15y. Table 2 presents the comparison of weight and height measurements to reference values among female study participants across different age of 11y, 12y, 13y, 14y and 15y. Thus, statistical significance can be seen in weight measurements at all age and height at 14 and 15years. While there is no statistical significance for height measurements at 11y, 12y and 13y among female participants. The figure 2 displays categorization of patients according to their gender and Tanner staging, which is a measure of sexual maturity. Here, males in tanner stage 1, 2, 3 and 4 are 53%, 29%, 17% and 1% respectively. While, females are 41%, 25%, 33% and 1% in Tanner stage 1, 2, 3 and 4 respectively.

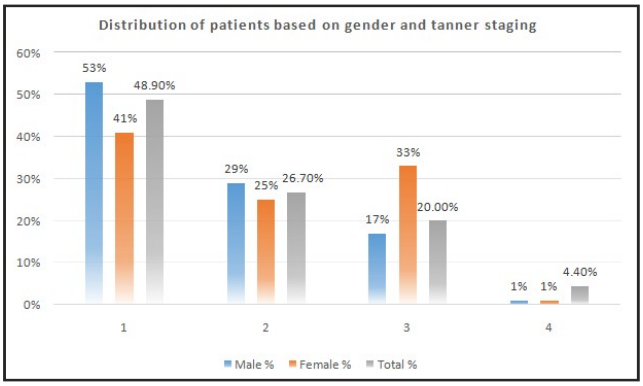

Figure 2. Distribution of patients based on gender and tanner staging

Table 1. Comparison of weight and height to reference value among male study participant

Age (Years)	Weight (kg) (Mean ± SD)	Reference Weight (kg)	p-value (Student's t-test)	Height (cm) (Mean ± SD)	Reference Height (cm)	p-value (Student's t-test)
11	30.0 ± 2.8	35 ± 8.9	0.013	135 ± 3.5	143 ± 7.6	0.002
12	30.3 ± 2.4	40 ± 10.0	0.005	138.8 ± 2.1	146 ± 8.1	0.003
13	35.3 ± 0.3	43 ± 11.3	0.018	148 ± 1.4	155 ± 9.0	0.09
14	35.2 ± 1.8	47 ± 12.1	0.002	148 ± 2.9	160 ± 9.0	0.006
15	40.4 ± 1.9	53 ± 12.1	0.016	162.6 ± 4.8	165 ± 7.9	0.197

Table 2. Comparison of weight and height to reference value among female study participant

Age (Years)	Weight (kg) (Mean ± SD)	Reference weight (kg)	p-value (Student's t-test)	Height (cm) (Mean ± SD)	Reference height (cm)	p-value (Student's t-test)
11	25.4 ± 2.1	34 ± 8.5	0.004	129.3 ± 8.8	143 ± 7.9	0.053
12	28.6 ± 0.0	40 ± 9.0	0.005	134.0 ± 0.0	146 ± 7.0	0.051
13	37.3 ± 0.0	43 ± 9.4	0.005	152.0 ± 0.0	152 ± 6.9	0.052
14	36.2±2.2	45±4.3	0.016	153.1±0.3	154.3 ±4.1	0.005
15	36.1 ± 7.7	48 ± 9.6	0.049	158.5 ± 9.3	156 ± 6.4	0.005

Table 3. Comparative analysis of age of patients in relation to the Indian reference age across various Tanner stages

Gender	Tanner staging (SMR)	No. of patients (n)	Age (Years) (Mean±SD)	Reference age (years)	p-value (Student's t-test)
Male	1	17	11.62±0.77	10.4±1.0	0.002
	2	9	14.63±0.52	11.3±1.2	0.001
	3	5	14.75±0.50	12.8±1.2	0.004
	4	1	16.0±0.0	14.5±0.7	0.005
Female	1	5	11.0±0.0	10.5±1.0	0.356
	2	3	13.5±2.12	10.2±1.1	0.272
	3	4	14.33±1.16	11.6±1.3	0.055
	4	1	15.0±0.0	13.5±1.2	0.012

Table 3 displays a comparative examination of patients' age in relation to the Indian reference age across different Tanner stages, categorized by gender. Thus, there is statistical significance in male gender in all Tanner stages where the males achieve delayed sexual maturity. While in female group statistical significance for delayed sexual maturity is seen only in tanner stage 4. Puberty is a transition from infancy to adulthood that involves physiological, somatic, and constitutional changes related to internal and external genitalia and secondary sex characteristics.[8]SCD adolescents face delayed puberty, vaso-occlusive menstrual discomfort, and underdiagnosed abnormal uterine bleeding.[9]A study that matched children with SCD to peers without SCD by Tanner Stage found that each stage lagged unaffected individuals by 2–4 years.[10] Early start of hydroxyurea therapy helps in reduction of early mortality[11] and normalizes growth parameters[12]. SCD adolescents look younger than their peers. This developmental delay disturbs parents, causes social issues, and threatens mental health.[13] The study conducted a comparison between the weight and height measurements of individuals diagnosed with sickle cell disease (SCD) in different age groups and the corresponding reference values. For 11-year-olds boys, the average weight was 85.7% of the reference weight, and this difference was statistically significant. Similarly, the average height was 94.4% of the reference height, and this difference was also statistically significant. For individuals aged 13, their weight was 82.0% of the standard weight, and although the difference was not statistically significant, their height was 95.5% of the standard height. Significant variations in weight and height were observed among girls in most age groups when compared to reference values, indicating disparities in growth among patients with Sickle Cell Disease (SCD). Significantly, when individuals were 15 years old, their average weight and height were noticeably lower than the standard values. This emphasizes the influence of SCD on growth patterns. Shah V et al.[14] found gender disparities in SCD patients. Male patients had lower mean weight and height than Indian boys, with substantial differences in specific age groups. Male SCD patients had a greater mean Tanner stage progression age than Indian reference children, indicating delayed sexual maturity. In several age groups, female weight inequalities were considerable, although height differences were not. Regarding sexual maturation, Serjeant et al. found delays in menarche in female SCD patients, with SS illness delaying menarche the greatest compared to controls. This supports previous findings that SCD patients mature sexually later than controls. The result also supports previous findings that SCD children and adolescents grow slower than healthy controls. SCD patients had reduced weight and height, showing that the condition affects growth and development.[15] In addition, Zemel B et al.[10] found a steady drop in growth indices in SCD children, emphasizing the disease's long-term impact on growth. The current study uses Tanner staging to investigate sexual maturity rating in sickle cell disease (SCD) patients in India. The results show notable differences in sexual maturation throughout all stages when compared to typical Indian reference ages. Across all stages, boys consistently show delayed maturation, with higher average ages, indicating the effect of SCD on pubertal timing. Girls, on the other hand, demonstrate less consistent patterns; in particular, some phases show considerable changes in average age when compared to the reference, suggesting complex impacts that may be related to the severity and course of treatment of the condition. The study emphasizes the necessity for specialized therapies to address the differences in sexual maturation rates among individuals with sickle cell disease (SCD). Furthermore, other research shows that SCD patients experience delayed sexual maturation in comparison to healthy controls, which validates the study's conclusions. These results are further supported by

studies[15–17] which show that both male and female SCD patients experience delayed puberty onset and progression. In addition, the Shah V et al.[14] study clarifies the clinical management of SCD patients, a considerable number of whom need blood transfusions. It's interesting to note that the majority of transfusion-dependent patients were in Tanner stage 1, which may have consequences for disease management and therapy approaches.

CONCLUSION

The current study offers significant understanding into the sexual development of sickle cell disease (SCD) patients in India. In all stages, male patients consistently showed delayed maturation; female patients showed less consistent patterns. These results highlight the complicated interactions between disease severity and treatment that may have an impact on sexual maturation in SCD patients. The study emphasizes the need for more research and customized therapies to address these differences and enhance our knowledge of how to better control pubertal development in people with sickle cell disease.

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