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Research Article

THYROID FUNCTION TEST IN SICKLE-CELL DISEASE

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ABSTRACT

Objective: This cross-sectional study aimed to evaluate the thyroid function (triiodothyronine [T3], thyroxine [T4], and thyroid-stimulating hormone [TSH] levels) in patients with sickle-cell disease (SCD).

Methods: This cross-sectional observational study was conducted in the general medicine department of the Veer Surendra Sai Medical College and Hospital, Burla, Sambalpur, Odisha (India). The investigation was performed in the sickle cell clinic, medical ward, and outpatient department of the institute. This study was conducted from November 2019 to October 2021. Sixty-eight patients with SCD were enrolled for assessing their thyroid function. The reference ranges for serum T4 (4.5–12 µg/dL), serum T3 (60–200 ng/dL), and TSH (0.3–5.5 uIU/mL) were defined to evaluate the thyroid function.

Results: The average TSH, mean T4 level, and mean T3 level among the patients were 4.02, 4.67, and 74.15, respectively. The incidence rates of hypothyroidism and euthyroid status were 23.5% and 76.5%, respectively. While 9.59 g/dL was the mean hemoglobin level, 11–16 g/dL was observed in 42.6% of patients compared to <11 g/dL in 57.4% of patients. Patients within the age group of 14-25 years had a higher incidence of hypothyroidism (62.5%). The differences in hypothyroidism between males and females were statistically insignificant (68.8% vs. 31.2%, p = 0.11).

Conclusion: Patients with SCD had clinically significant reductions in T3 and T4 levels. In addition, higher levels of TSH and reductions in endogenous T3/T4 levels were observed in male patients. Overall, SCD was associated with a higher incidence of hypothyroidism.

Keywords: Sickle-cell anemia, Sickle-cell disease, Hypothyroidism, Thyroid function test.

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INTRODUCTION

Hemoglobinopathies are conditions indicating abnormalities in the function, production, and structure of hemoglobin [1]. The replacement of the glutamate by the sixth valine triggers the beta globulin gene's point mutation, which eventually results in hereditary structural hemoglobinopathy. The first disorder based on the hemoglobulin synthesis abnormality was reported in Chicago by James Herrick in 1910 [2]; this abnormality was named sickle cell anemia in 1922 [3]. The potential complications of sickle-cell disease (SCD) include chronic organ damage, organ dysfunction, acute/chronic tissue anemia, small vessel (intermittent) occlusion, hemolysis, and abnormal production of hemoglobulin [4]. The sickling of hemoglobulin reduces its oxygen binding capacity, which eventually results in anemia, hemolytic crisis, and organ injury. Patients with SCD experience a high risk of mortality, an increase in disability-adjusted life years due to organ dysfunction, and reduced overall survival [5]. Individuals with the homozygous HbSS are highly predisposed to SCD [6], whereas the highest prevalence of this condition is recorded in the Indo-Arabian subcontinent and sub-Saharan Africa [7]. In India, SCD was first described by Dunlop and Mujumdar; however, its prevalence was first reported in 1967 by Raman *et al.* in Western Odisha [8].

Sickling incidence at birth is reportedly low in most scenarios; however, it increases gradually over the period of several months [9]. The vaso-occlusive crisis develops in individuals with high levels of HbS. Infants and children in Africa experience a high incidence of deaths due to homozygous SCD [10]. Contrarily, patients with homozygous SCD in other parts of the world survive for 35–66 years. The evidence further reveals a comparable incidence of SCD in female and male patients [11]. Globin is a protein of 64,000Da that constitutes the major portion of hemoglobin [12]. In addition, the heme moiety integrates with each of the two polypeptide chains of globin. The quaternary structure of hemoglobin is based on a complex helical arrangement of alpha, beta, and delta chains. While 2-alpha and 2-beta chains individually constitute HbA, their combination defines the structure of HbA2 [13]. The potential complications of SCD include vascular occlusion, infection, anemia, and hemolysis [14]. Infections in patients with SCD increase the risk of comorbidities and mortality. However, mortality in the elderly patients with SCD is predominantly attributed to stroke and acute chest syndrome [15]. The clinical presentation of SCD includes a steady state, acute crisis, and chronic complications. The steady state is associated with the incidence of gallstones, splenomegaly, jaundice, and stunted growth [16]. The acute crisis elevates the risk of acute renal failure and splenic hypofunction; however, the fatal complications include acute intrahepatic cholestasis and acute hepatic sequestration [17]. The chronic complications of SCD include chronic kidney disease, pulmonary hypertension, cerebrovascular accident, and vision loss [18].

It is important to determine the thyroid function changes in SCD to predict the risk and incidence of its acute and chronic complications. Findings from the recent studies demonstrate a clinically significant correlation between SCD and elevation in free T4 levels that significantly impacts cardiac function and increases the risk of sudden cardiac death [19]. The abnormal functioning of cardiomyocytes in SCD is probably due to the abnormal levels of thyroid hormones. However, the findings in the contemporary literature do not provide definitive diagnostic parameters to calculate the risk of possible comorbid conditions in SCD. This cross-sectional study aimed to fill in this gap by investigating the thyroid function in patients with SCD.

METHODS

Study design

This cross-sectional observational study was conducted in the general medicine department of the Veer Surendra Sai Medical College and Hospital, Burla, Sambalpur, Odisha (India). The investigation was performed in the sickle cell clinic, medical ward, and outpatient department (OPD) of the institute. This study was conducted from November 2019 to October 2021. The study population was comprised patients with SCD (n=68) who received treatment in the medical ward, sickle cell clinic, and medicine OPD. The convenience sampling approach was used to recruit the study participants.

Inclusion and exclusion criteria

Patients with a definitive SCD diagnosis were included in this study. The diagnostic confirmation was done by high-performance liquid chromatography, hemoglobin electrophoresis, and sickling test. However, patients with sickle cell trait, sickle beta thalassemia, sickle cell-hemoglobin C, diabetes mellitus, hypertension, and chronic kidney disease were excluded from this study.

Data and sample collection

The data collection sources included the patient's detailed clinical history, clinical examination findings, bed head tickets, sickling slide test, hemoglobin electrophoresis results, high-performance liquid chromatography outcomes, and radioimmunoassay for thyroid-stimulating hormone (TSH), thyroxine (T4), and triiodothyronine (T3) levels.

This study enrolled 68 patients who fulfilled the eligibility parameter. The clinical variables were analyzed after collecting 5 mL of the patient's blood through venous access. Total T4, total T3, and TSH levels were calculated after serum separation. The reference ranges for serum T4 (4.5–12 μg/dL), serum T3 (60–200 ng/dL), and TSH (0.3–5.5 uIU/mL) were defined to evaluate the thyroid function. DisSys Die Patientennahe Labordiagnostik (POCT) apparatus has been used in our study for performing the thyroid function test.

Data analysis

The statistical analysis of the patient data was performed by IBM SPSS-27 version. The means, standard deviations, and percentages of T3, T4, and the TSH were calculated for examining the thyroid function [20].

RESULTS

This study included 68 patients with SCD; of them, 51.5% (n=35) were males and 48.5% (n=33) were females. The mean age of the patients with SCD was 24.38 years (standard deviation: 6.82). Patients between the age group of 45–60 years were 1.5% of the total study population. In addition, 4.4% of patients were in the age range of 35–45 years, and 29.4% of them were in the age group of 25–35 years. However, most of the patients (64.7%) belonged to the age group of 14–25 years.

The laboratory assessments and clinical examinations aimed to determine the overall health status of the study participants. Table 1 describes the overall clinical signs of patients with SCD. While hypotension was recorded in 29.4% of patients, normal systolic blood pressure was observed in 70.6% of patients. Of note, no patient had abnormal diastolic blood pressure. Most patients (92.6%) had a normal heart rate, whereas tachycardia was reported in 7.4% of the participants. Normal respiratory rate was reported in 60.3% of patients with SCD, whereas tachypnea was observed in 39.7% of participants. Almost 7.4% of patients had <95% of oxygen saturation level.

Table 2 demonstrates the hematological profile of patients with SCD. The blood glucose levels of most patients (98.5%) were reportedly normal; however, a random blood sugar of >150 g/dL was observed in one patient. While 9.59 g/dL was the mean hemoglobin level, 11–16 g/dL was observed in 42.6% of patients compared to <11 g/dL in 57.4% of patients. Overall, 7.4 of patients had <1.5 lac platelet count, whereas 8.8% of them had a platelet count of >4 lac. Most (83.8%) participants had a platelet count within the range of 1.5–4 lac. The total leukocyte count was observed as >10,000, 4,000–10,000, and <4000 in 29.4%, 66.2%, and 4.4% of patients. While 30.82 was the mean erythrocyte sedimentation rate, the hematocrit, mean corpuscular hemoglobin concentration, mean corpuscular hemoglobin, and mean corpuscular volume values were 34.19, 34.29, 26.38, and 74.62, respectively.

Table 3 presents the thyroid profile of the patients with SCD. The average TSH, mean T4 level, and mean T3 level among the patients were 4.02, 4.67, and 74.15, respectively. Table 1 depicts the thyroid status of patients with SCD. The incidence rates of hypothyroidism and euthyroid status were 23.5% and 76.5%, respectively. Tables 4 and 5 depict the age-based and sex-wise incidences of hypothyroidism in patients with SCD.

DISCUSSION

This cross-sectional study was performed on 68 patients with SCD, including 48.5% of females and 51.5% of males, respectively. The overall results indicated the mean values of T4 (4.67±0.86/range: 2.08–5.93), T3 (74.15/range: 2.08–5.93), and TSH (4.02±2.33/range: 2.01–11.96).

Table 1: Thyroid status of patients with SCD

Thyroidism	n=68
Euthyroidism	52 (76.5%)
Hypothyroidism	16 (23.5%)

Table 2: Hematological profile patients with SCD

Variables	n=68
RBS_Class	
<70 mg/dL	0 (0.0%)
70–140 g/dL	67 (98.5%)
>140 g/dL	1 (1.5%)
HB	
Mean (SD)	9.59 (2.47)
Range	3.10–13.60
HB_class	
<11 gm/dL	39 (57.4%)
11–16 g/dL	29 (42.6%)
>16 g/dL	0 (0.0%)
TPC_class	
<1.5 lac	5 (7.4%)
1.5–4 lac	57 (83.8%)
>4 lac	6 (8.8%)
TLC_class	
<4000	3 (4.4%)
4,000-10,000	45 (66.2%)
>10,000	20 (29.4%)
MCV	
Mean (SD)	74.62 (7.55)
Range	55.00–89.00
MCH	
Mean (SD)	26.38 (3.98)
Range	16.00–35.00
MCHC	
Mean (SD)	34.29 (2.81)
Range	28.00–45.00
HCT	
Mean (SD)	34.19 (8.13)
Range	18.00–52.00
ESR	
Mean (SD)	30.82 (29.45)
Range	5.00–140.00

SD: Standard deviation, SCD: Sickle-cell disease, MCV: Mean corpuscular volume, MCH: Mean corpuscular hemoglobin, MCHC: Mean corpuscular hemoglobin concentration, ESR: Erythrocyte sedimentation rate, RBS: Random blood sugar, HB: Haemoglobin, TLC: Total leucocyte counts

Table 3: Thyroid function test outcomes

Variables	n=68
T3	
Mean (SD)	74.15 (22.79)
Range	15.59–105.82
T4	
Mean (SD)	4.67 (0.86)
Range	2.08–5.93
TSH	
Mean (SD)	4.02 (2.33)
Range	2.01–11.96

SD: Standard deviation, T3: Triiodothyronine, T4: Thyroxine, TSH: Thyroid stimulating hormone

Table 4: Age-wise incidences of hypothyroidism among the study subjects

Age group	Euthyroid (n=52)	Hypothyroidism (n=16)	Total (n=68)	p-value
14–25 years	34 (65.4%)	10 (62.5%)	44 (64.7%)	0.92
25–35 years	15 (28.8%)	5 (31.2%)	20 (29.4%)	
35–45 years	2 (3.8%)	1 (6.2%)	3 (4.4%)	
45–60 years	1 (1.9%)	0 (0.0%)	1 (1.5%)	

Table 5: Sex-wise incidences of hypothyroidism among the study subjects

Sex	Euthyroid (n=52)	Hypothyroidism (n=16)	Total (n=68)	p-value
Female	28 (53.8%)	5 (31.2%)	33 (48.5%)	0.11
Male	24 (46.2%)	11 (68.8%)	35 (51.5%)	

While most (76.5%) of the patients were euthyroid, hypothyroidism was observed in 23.5% of the participants. Patients within the age group of 14-25 years had a higher incidence of hypothyroidism (62.5%). The differences in hypothyroidism between males and females were statistically insignificant (68.8% vs. 31.2%, p=0.11).

The findings of this study concord with the outcomes of Soliman *et al*. that define the clinical correlation of central/primary hypothyroidism in patients with SCD based on their anemia severity and age [21]. In addition, poor chelation is observed in patients with elevated ferritin levels [22]. The findings of El-Alfy *et al*. reveal higher pulsatility and resistance indices and reduced volume of thyroid in patients with SCD [23]. The results of Özen *et al*. indicate a marked reduction in the endocrine functions in SCD cases [24]. It is important to delineate all possible causes of hypothyroidism in SCD to understand its possible impact on endocrine dysfunction. The findings by Phillips Jr *et al*. indicate hypothyroidism in patients with SCD with several transfusions, which may have a role in disrupting the endocrine function [25]. A recent study demonstrates the possible association between thyroid disease and pulmonary arterial hypertension [26]. This finding indicates the need for examining the pulmonary blood pressure in SCD cases to improve the differential assessment.

Progressive deterioration of endothelial dysfunction is observed in patients with SCD, which eventually lowers the thyroid volume [23]. Literature reveals 10% and 12% of incidences of subclinical hypothyroidism and primary hypothyroidism, respectively, in SCD cases [27]. The outcomes of the thyroid function test do not differ and remain comparable between patients with SCD irrespective of their genotypes [28]. Findings from several studies indicate significant reductions in thyroid volume in patients with SCD who contract viral hepatitis C [29]. They also reveal the absence of a clinical correlation between iron overload (based on liver iron and serum ferritin levels) and thyroid Doppler variables [23]. However, vasculopathy and microcirculation in the thyroid may deteriorate its physiology in SCD cases.

The inconsistent findings of the thyroid function test in SCD cases indicate the need for further diagnostic assessments for improving clinical outcomes. It is important to rule out the possible impact of comorbidities on the thyroid function of patients with SCD. Clinically significant elevation in the TSH and reduction in endogenous T3 levels in SCD cases also correlate with the SS genotype of the male patients [30]. In addition, SCD is possibly associated with high levels of the TSH-releasing hormone, resulting in abnormal accumulation of TSH, which eventually leads to thyroid dysfunction [19]. Findings from recent studies indicate abnormal thyroid function in patients with high iron deposits, which indicates the possible impact of cellular damage due to transfusional hemosiderosis on the thyroid function of patients with SCD [21]. However, most patients with SCD do not develop pituitary-thyroid axis abnormality [31]. In addition, the abnormal levels of T3 and T4 in SCD indicate inconsistencies in the thyroid-binding levels of the globulin [32]. These outcomes substantiate the requirement of the thyroid function test in SCD to determine the clinical outcomes.

CONCLUSION

This study presented the outcomes of the thyroid function test in patients with SCD. Marked reductions in T3 and T4 levels correlated with SCD pathology. Importantly, higher levels of TSH and reduced endogenous T3/T4 levels were observed in male patients. In addition, a higher incidence of hypothyroidism was observed in patients with SCD. Since contemporary literature does not elaborate on the thyroid function etiology in SCD cases, future studies should reinvestigate our findings and determine the pathogenesis and clinical complications of hypothyroidism in patients with SCD manifestations.

REFERENCES

1. Kohne E. Hemoglobinopathies: Clinical manifestations, diagnosis, and treatment. Dtsch Ärztebl Int 2011;108:532-40.
2. Savitt TL, Goldberg MF. Herrick's 1910 case report of sickle cell anemia. The rest of the story. JAMA 1989;261:266-71.
3. Mason VR. Landmark article Oct. 14, 1922: Sickle cell anemia. By V.R. Mason. JAMA 1985;254:1955-7.
4. Ilesanmi OO. Pathological basis of symptoms and crises in sickle cell disorder: Implications for counseling and psychotherapy. Hematol Rep 2010;2:e2.
5. Lubeck D, Agodoa I, Bhakta N, Danese M, Pappu K, Howard R, *et al*. Estimated life expectancy and income of patients with sickle cell disease compared with those without sickle cell disease. JAMA Network Open 2019;2:e1915374.
6. Adekile A. The genetic and clinical significance of fetal hemoglobin expression in sickle cell disease. Med Princ Pract 2021;30:201-11.
7. Williams TN. Sickle cell disease in sub-Saharan Africa. Hematol Oncol Clin North Am 2016;30:343-58.
8. Raman V, Seshadri T, Joice SV, Srinivas PN. Sickle cell disease in India: a scoping review from a health systems perspective to identify an agenda for research and action. BMJ Global Health 2021;6:e004322.
9. Wastnedge E, Waters D, Patel S, Morrison K, Goh MY, Adeloye D, *et al*. The global burden of sickle cell disease in children under five years of age: A systematic review and meta-analysis. J Glob Health 2018;8:021103.
10. Egesa WI, Nakalema G, Waibi WM, Turyasiima M, Amuje E, Kiconco G, *et al*. Sickle cell disease in children and adolescents: A review of the historical, clinical, and public health perspective of sub-Saharan Africa and beyond. Int J Pediatr 2022;2022:3885979.
11. Ceglie G, Di Mauro M, De Jacobis IT, de Gennaro F, Quaranta M, Baronci C, *et al*. Gender-related differences in sickle cell disease in a pediatric cohort: A single-center retrospective study. Front Mol Biosci 2019;6:140.
12. Hardison RC. Evolution of hemoglobin and its genes. Cold Spring Harb Perspect Med 2012;2:a011627.
13. Villegas A, González FA, Nieto JM, de la Fuente-Gonzalo F, Martínez R, Torrejón MJ, *et al*. Haemoglobinopathies that occur with decreased HbA2levels: A gene mutation set involving the δ gene at a Spanish centre. J Clin Pathol 2017;70:75-80.
14. Ochocinski D, Dalal M, Black LV, Carr S, Lew J, Sullivan K, *et al*. Life-threatening infectious complications in sickle cell disease: A concise narrative review. Front Pediatr 2020;8:38.
15. Sysol JR, Machado R. Sickle cell disease and acute chest syndrome:

Epidemiology, diagnosis, management, outcomes. In: Hematologic Abnormalities and Acute Lung Syndromes. Respiratory Medicine. Cham: Humana Press; 2017. p. 67-87.
16. Shah R, Taborda C, Chawla S. Acute and chronic hepatobiliary manifestations of sickle cell disease: A review. World J Gastrointest Pathophysiol 2017;8:108-16.
17. Khan A, Nashed B, Issa M, Khan MZ. Sickle cell intrahepatic cholestasis: Extremely rare but fatal complication of sickle cell disease. Cureus 2022;14:e22050.
18. Ogu UO, Badamosi NU, Camacho PE, Freire AX, Adams-Graves P. Management of sickle cell disease complications beyond acute chest syndrome. J Blood Med 2021;12:101-14.
19. Yamakawa H, Kato TS, Noh JY, Yuasa S, Kawamura A, Fukuda K, *et al*. Thyroid hormone plays an important role in cardiac function: From bench to bedside. Front Physiol 2021;12:606931.
20. Shokripour M, Imanieh MH, Garayemi S, Omidifar N, Yeganeh BS, Althabhawee F. Thyroid stimulating hormone, T3 and T4 population-based reference range and children prevalence of thyroid dysfunction: First report from South of Iran. Iran J Pathol 2022;17:427-34.
21. Soliman AT, De Sanctis V, Yassin M, Wagdy M, Soliman N. Chronic anemia and thyroid function. Acta Biomed 2017;88:119-27.
22. Poggiali E, Cassinerio E, Zanaboni L, Cappellini MD. An update on iron chelation therapy. Blood Transfus 2012;10:411-22.
23. ElAlfy MS, El-Sherif NH, Sakr HM, El Ashkar MN. Thyroid hemodynamic alterations in Egyptian patients with sickle cell disease: Relation to disease severity, total body iron and thyroid function. Expert Rev Hematol 2019;12:589-96.
24. 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;30:25-31.
25. Phillips G Jr., Becker B, Keller VA, Hartman J 4th. Hypothyroidism in adults with sickle cell anemia. Am J Med 1992;92:567-70.
26. Pi H, Rayner SG, Ralph DD, Nolley S, Barros LM, Steinberg ZL, *et al*. Thyroid-stimulating hormone and mortality in pulmonary arterial hypertension. BMJ Open Respira Res 2022;9:e001348.
27. Calissendorff J, Falhammar H. To treat or not to treat subclinical hypothyroidism, what is the evidence? Medicina (Kaunas) 2020;56:40.
28. Honsel V, Khimoud D, Ranque B, Offredo L, Joseph L, Pouchot J, *et al*. Comparison between adult patients with sickle cell disease of sub-Saharan African origin born in metropolitan France and in sub-Saharan Africa. J Clin Med 2019;8:2173.
29. El-Feki MA, Abdalla NH, Atta MI, Ibrahim AA. Serum level of thyroid hormones in patients with chronic hepatitis C virus infection. Open J Endocr Metab Dis 2016;6:126-34.
30. Hagag AA, El-Asy HM, Badraia IM, Hablas NM, El-Latif AE. Thyroid function in Egyptian children with sickle cell anemia in correlation with iron load. Endocr Metab Immune Disord Drug Targets 2019;19:46-52.
31. Garadah TS, Jaradat AA, Alalawi ME, Hassan AB. Hormonal and echocardiographic abnormalities in adult patients with sickle-cell anemia in Bahrain. J Blood Med 2016;7:283-9.
32. Chakravarthy V, Ejaz S. Thyroxine-binding globulin deficiency. In: StatPearls. Treasure Island, FL: StatPearls Publishing; 2022.