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Sickle cell disease and biological assessment of the thyroid gland in Lubumbashi

Tshibumbu Kabeya Edouard [1,*], Kasamba Ilunga Eric [1], Lungu Anzwal Philomene [1], Balaka Ekwalanga Michel [1], Shongo Ya Pongombo Mick [2], Kazadi Lubobo Claude [1] and Ndibualonji Badibanga Victor [3]

[1] *Department of Biomedical Sciences, Faculty of Medicine, University of Lubumbashi, DR Congo.*
[2] *Department of Pediatrics, Faculty of Medicine, University of Lubumbashi, DR Congo.*
[3] *Department of Biochemistry, Faculty of Veterinary Medicine, University of Lubumbashi, RD Congo.*

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Abstract

Introduction: Sickle cell disease is an inherited red blood cell disorder that leads to oxidative stress with the consequence of damage to certain organs, including the thyroid.

Objective: To evaluate changes in serum concentrations of triiodothyronine (T_3), tetra-iodothyronine (T_4) and thyroid-stimulating hormone (TSH) in subjects with sickle cell disease in the city of Lubumbashi.

Methods: This study examined indicators of energy metabolism and a marker of oxidative stress in sickle cell anemia children attending "The Sickle Cell Care Center (C-fare) ". (n=64) and healthy control group (n = 64). The serum obtained after centrifugation of venous blood sample, was used for evaluate T_3, T_4 and TSH concentration. Mean values obtained from patients and the control group were statistically compared using the Student's t test.

Results: Mean values of T_3, T_4 and TSH in sickle cell anemia children were respectively 1.91 ± 0.60 ng/L; 119.73 ± 25.32 nmol/L and 2.99 ± 1.48 mIU/L. In control group, these values were 2.71 ± 1.22 ng/L; 130.96 ± 28.42 nmol/L and 2.18 ± 5.05 mIU/L respectively. The mean values of T_3 and T_4 were significantly lower ($p < 0.0001$) while the mean value of TSH was significantly higher ($p < 0.01$) in patients compared to the control group.

Conclusion: This study demonstrates that sickle cell disease shows greater incidence of hypothyroidism characterized by a significant decrease in T3 and T 4 with a significant increase in TSH.

Keywords: SS Anemia; Hemolysis; Oxidative stress; Thyroid Function; Lubumbashi

1. Introduction

Sickle cell disease (SCD), recognized since 2006 by the World Health Organization (WHO) as a global public health problem (1), is an autosomal recessive hereditary disease (2-4) characterized by the synthesis abnormal sickle cell hemoglobin S (βs, HbS) (5, 6). It is a hemoglobinopathy that causes major dysfunction of red blood cells (7). Every year, more than 500,000 newborns are born with major sickle cell syndrome worldwide (8). African data show that 5% of child deaths that are under 5 years old, are associated with SS disease (9) which represent nearly 75% of all people affected by the disease in the world (10) and this represents a heavy burden for sub-Saharan Africa (11). In Central Africa where Congo is situated, 1 in 30 newborns has sickle cell disease (4). The erythrocyte anomalies in SCD manifest in hemolytic anemia (12, 13) and cycles of microvascular vaso-occlusion leading to end-organ ischemia-reperfusion injury and infarction (14). Vaso-occlusive events and intravascular hemolysis promote inflammation and redox instability that lead to progressive small- and large-vessel vasculopathy that may be associated with defects in nitric

* Corresponding author: Tshibumbu Kabeya Edouard.

oxide bioavailability, abnormal interactions between sickled red blood cells, cells endothelial cells, platelets and leukocytes, and elevated oxidative stress (15, 16).

The physiological response to stress includes activation of the central nervous system, the endocrine and immune systems (17).

Stress-induced physiological and endocrine alterations, disruptions in functional (e.g. clinical parameters), biochemical (e.g. hormones), metabolic systems become inevitable and, consequently, alterations in metabolic biomarkers (metabolites, enzymes, hormones) also result (18).

The aim of this work was to evaluate thyroid function in children with sickle cell anemia by assessing their biological status compared to non- sickle cell patients.

2. Material and Methods

2.1. Site of research

The C-Fare medical center was the site where blood samples were collected from sickle cell patients. The blood samples of the control group were collected at the laboratory of the University Teaching Hospital of Lubumbashi (Cliniques Universitaires de Lubumbashi), this is where all the biochemical analysis were performed. Lubumbashi, capital of the Haut-Katanga province in the Democratic Republic of Congo, covers an area of 747 km ^{2} (19).

2.2. Study population

This study was conducted on 64 children with sickle cell anemia (Hb SS) with their age ranging from 1 and 23 years (mean age value of 10.20 ± 3.14 years) and 64 control group with their age fluctuating from 2 to 21 years (mean value age of 11.59 ± 4.14). The selection was made without distinction of race, tribe or social class.

2.2.1. The exclusion criteria were

Children who have not been diagnosed with homozygous sickle cell disease by hemoglobin electrophoresis and those who have been transfused in less than 3 months

Children in a period of sickle cell crisis.

The study was approved by the ethics committee of the University of Lubumbashi (Approval UNILU/CEM/100/2022 of June 3, 2022) and each participant signed the informed consent form.

2.3. Equipment used

- Finecare analyzer
- Centrifuge (Horizon),
- Water bath (Memmert),
- Fridge (Liebherr),
- Mixer (Cat rem 5) ,
- Micropipettes (Eppendorf),
- Bowls,
- Stopwatch,
- tubes with red cap ,
- The BD Vacutainer system (needle, body and collection tube)
- tourniquet,
- Wadding,
- Alcohol,
- Yellow and blue tips.

2.4. Methods

2.4.1. Specimen collection and handling

Four ml of venous blood were collected using sterile needles through gentle venipuncture after sterilization of puncture site by alcohol, and collected samples were put into test tubes without anticoagulant at the C-fare Medical Center for sickle cell subjects and at the University teaching hospital of Lubumbashi for control group. The blood samples collected at the C-fare Medical Center were immediately (the same day) sent to the University Teaching Hospital of Lubumbashi for analysis. The blood was centrifuged at 2500 rpm for ten minutes before any laboratory analysis.

2.5. Laboratory analysis

2.5.1. TSH dosage

The thyroid-stimulating hormone blood assessment was performed using the Finecare™ rapid quantitative test. TSH rapid quantitative test which is based on the fluorescence immunoassay technique, uses a sandwich immunodetection method. When the sample is added to the sample well of the test cartridge, the fluorescently labeled TSH detector antibodies on the sample pad bind to the TSH antigens in the blood sample and form a immune complex. As the complexes migrate onto the nitrocellulose matrix of the test strip by capillary action, the TSH-detecting antibody complexes are captured by TSH antibodies that have been immobilized on the test strip. So, the more antigen TSH in the blood sample, the more complexes build up on the test strip. The fluorescence signal intensity of the detector antibodies reflects the amount of captured TSH antibodies.

2.5.2. T_3 dosage

The T_3 blood assay was carried out by the Finecare™ T_3 rapid quantitative test which is based on the fluorescence immunoassay technique. It uses a competitive immunodetection method. When the sample is added to the sample well of the test cartridge, the fluorescent marker T_3 detector antibodies bind to the T3 antigens in the blood sample and form immune complexes. As the complexes migrate onto the nitrocellulose matrix by the action of capillarity, they cannot be captured by the T_3 antigens that were immobilized during the undressed test. But excess fluorescently labeled anti-T_3 detector antibodies are captured. Thus, the more T_3 there is in the blood, the less fluorescence labeling not linked to antibodies accumulated on the test strip. The signal intensity of the T_3 detector antibodies reflects the amount of antigens that are processed in the FinecareTM FIA system to determine the concentration of T_3 in the blood.

2.5.3. T_4 Dosage

The blood T_4 assay was carried out by the Finecare™ T_4 rapid quantitative test which is based on the fluorescence immunoassay technique. It uses a competitive immunodetection method. When the sample is added into the sample well of the test cartridge, the fluorescent marker T_4 detector antibodies bind to the T_4 antigens in the blood sample and form an immunity complex. As the complexes migrate onto the nitrocellulose matrix by the action of capillarity, they cannot be captured by the T_4 antigens that were immobilized in the undressed assay. But excess fluorescently labeled anti-T_4 detector antibodies are captured. Thus, the more T_4 present in the blood, the less fluorescence labeling unrelated to antibodies accumulated on the test strip. The signal intensity of T_4 detector antibodies reflects the amount of antigens that are processed in the Finecare TM FIA system to determine the concentration of T_4 in the blood.

2.6. Statistical analyzes

All data were entered and analyzed using Epi info software. Data are presented as mean ± standard deviation. Statistical differences in blood levels of different hormones (T_3, T_4, and TSH) between sickle cell patients and controls were determined using the *t* -test or Wilcoxon signed-rank test for continuous data.

Differences between patient and control data were considered statistically significant at a value of < 0.05.

3. Results

Table1 shows a statistically significant difference between controls and sickle cell patients with regard to T_3 (2.71 ± 1.21 vs 1.91 ± 0.60 ng/L, $P < 0.0001$), T_4 (5130.96 ± 28.42 vs 119.73 ± 25.32 nmol/L, $P < 0.05$) and TSH (2.18 ± 5.05 vs 2.99 ± 1 .48 mIU/L, P=0.0001) while there is no statistically significant difference between the two groups with regard to age (10.20 ± 3.14 vs 11.59 ± 4.14 years, $P > 0.05$).

Table 1 The mean serum T3, T4, and TSH in sickle cell patients and control group**.**

	Control group	**Sickle cell patients**	**p-value**	**p-value**
Age	10.20 ± 3.14	11.59 ± 4.14	0.08730257	> 0.05
T_3 (ng/L)	2.71 ± 1.21	1.91 ± 0.60	5.01623E-06	< 0.0001
T_4 (nmol/L)	130.96 ± 28.42	119.73 ± 25.32	0.019783447	<0.05
TSH (mIU/L)	2.18 ± 5.05	2.99 ± 1.48	5.18944E-05	< 0.0001

4. Discussion

The present study showed that in sickle cell patients the mean blood levels of T_3 (1.96 ± 0.67 ng/L) and T_4 (118.28 ± 19.19 nmol/L) were significantly lower than the control group (p = 0.00001 for T3 and p = 0.01978 for T_4). Conversely, TSH value (2.95 ± 1.51 mIU/L) was significantly higher in sickle cell patients (p-value = 0.00005), and this regardless of gender. Among sickle cell patients, 20.31% had a T_3 and T_4 level below the norms, and a TSH level above the norms, thus suggesting hypothyroidism. These results are consistent with findings from Kaudha et al. (2020) who performed a research at Makerere University Mulago Hospital in Uganda and found that 18.1% of children with SS anemia aged 6 months to 17 years had subclinical hypothyroidism (1). In contrast, the study carried out in 2008 in Omani patients with major transfusion-dependent homozygous beta-thalassemia who consulted in the thalassemia clinic at the Royal Hospital showed that primary hypothyroidism was present in only 1 patient (3.3%) (20). In addition, Özen et al. (2013) detected hypothyroidism in 6% of child and adolescent sickle cell patients in Turkey (21). The study carried out by Garadah et al. (2016) assessing the thyroid dysfunction in vivo showed a 7% incidence of hypothyroidism, with low levels of free T_4 and high levels of TSH (22). Furthermore, a study evaluating thyroid function in ninety children with homozygous sickle cell disease (SS), in forty-five children with heterozygous sickle cell disease (AS), and in 162 control children carrying AA genotype hemoglobin showed the serum thyroxine levels were not significantly different in the three groups. The distribution of individual thyrotropin (TSH) values showed that only 11% of HbSS subjects had values below the 95% confidence limits compared to HbAA controls. However, the mean TSH level was significantly lower in HbSS than in the other two groups of children (23) contrary to our results. Parshad et al., (1989) demonstrated that male sickle anemia patients had significant lower T_3 levels and higher TSH levels than the control group (24). However, normal thyroid function was preserved in children with iron deficiency anemia, but three of the nine children had minor abnormalities in hypothalamopituitary function (25).

The etiology of thyroid dysfunction in sickle cell disease is unclear; however, although Ashraf et al., (2017) showed that the etiology of primary thyroid insufficiency may be a transfusional hemosiderosis and subsequent cellular damage to the thyroid gland (26), despite the findings of El-Hazmi (1992) who found that the levels of T_3 and T_4 do not have significant differences between sickle cell patients and controls (27).

5. Conclusion

The current study shows that hypothyroidism is not a rare event in sickle cell patients in a stationary phase and its prevalence is 20.31% in our environment. This study may pave the way for further investigations into thyroid function by subsequent studies aimed to clarify the interaction between iron overload, the oxidative stress, and hypothyroidism in sickle cell anemia subjects in crisis phase or otherwise.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

Statement of informed consent

Informed consent was obtained from all individual participants included in the study.

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