VIA MEDICA

ORIGINAL ARTICLE

Int Marit Health
2024; 75, 1: 43–48
10.5603/imh.99311
www.intmarhealth.pl

ISSN 1641-9251
eISSN 2081-3252

Sickle cell disease in the Zanzibar Archipelago, the Republic of Tanzania

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ABSTRACT

Background: *Sickle cell disease (SCD) is one of the most severe haemoglobinopathies, a group of blood disorders, typically inherited. The condition affects over 7.7 million people globally and results in more than 370,000 deaths per year. The highest morbidity and mortality rates are seen in Africa and most children with SCD are born in Tanzania. The available literature on SCD morbidity in Tanzania focus primarily on the residents of the mainland, while there is little data available on SCD morbidity among residents of the Tanzanian islands in the Indian Ocean. The aim of the present study was to confirm the presence of sickle cell disease among residents of the Zanzibar Archipelago.*

Material and methods: *The study group consisted of 27 people, residents of Pemba Island in the Zanzibar Archipelago, aged between 2 months and 26 years old, whose at least one parent has been diagnosed with sickle cell anaemia. Blood samples collected from the study participants were tested using HemoTypeSC™, a rapid, point-of-care diagnostic test. The tests were performed at the Amal Hospital (Chake Chake town, Pemba Island) in June 2023.*

Results: *Sickle cell disease was diagnosed in 11 study subjects (40.7%); their haemoglobin concentration ranged between 6.6 and 8.5 g/dL. The presence of the sickle cell trait (HbAS phenotype) was confirmed in 14 patients (51.9%). Only two of the tested patients had normal haemoglobin phenotype.*

Conclusions: *The results of the present study support the necessity to introduce large-scale population-based screening for SCD in the Zanzibar Archipelago, especially in infants whose family members have sickle cell anaemia. The introduction of such a programme will help monitor the number of new SCD cases in the region and may potentially reduce infant mortality due to SCD as well as minimize complications from SCD in older children through the adoption of effective disease prevention measures.*

(Int Marit Health 2024; 75, 1: 43–48)

Keywords: haemoglobinopathy, sickle cell disease, anaemia, Tanzania

INTRODUCTION

According to the World Health Organization (WHO) sickle cell disease (SCD) is one of the most severe haemoglobinopathies, a group of blood disorders that are typically inherited. SCD affects over 7.7 million people globally and results in more than 370,000 deaths each year [1]. Approximately 80% of the global number of SCD cases are reported in Sub-Saharan Africa. Sickle cell disease is a clinical syndrome which results from the presence of abnormal HbS haemoglobin, an oxygen-carrying protein which is found in all red blood cells. SCD is caused by a point mutation, a change affecting a single nucleotide encoding the β-globin chain of haemoglobin (Hbβ). SCD is a pathology affecting the red blood cells (RBCs take

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Received: 8.02.2024 Accepted: 16.02.2024

the characteristic form of a sickle) which is a direct consequence of a gene defect consisting in the substitution of a single nucleotide in the amino-acid codon, which results in the transformation of the glutamine codon into the valine codon. The valine is hydrophobic and therefore attracts hydrophobic sites of the adjacent β chains, thus facilitating polymerization of haemoglobin molecules [2]. Once oxygen is delivered to the tissues, the mutant HbS haemoglobin polymerizes into fibres that distort the red blood cells into the sickle shape and block the blood flow in blood vessels causing acute, severe pain known as the sickle cell crisis [3]. Polymerization of deoxygenated HbS haemoglobin causes vascular occlusion which then leads to secondary processes such as haemolysis, anaemia or vasculopathy. The resulting ischaemic injury is associated with the production of reactive oxygen species and the activation of endothelial cells, neutrophils, monocytes and platelets, and leads to chronic inflammation. In addition, depleted production of nitric oxide causes endothelial dysfunction. These mechanisms result in chronic organ damage, such as pulmonary hypertension, aseptic bone necrosis, chronic lung disease, acute kidney injury, hepatic crisis, cholecystitis, stroke, multiple organ failure [4, 5]. Clinical manifestations of SCD usually present at 5–6 months of age. SCD is associated with high mortality and effective treatment relies heavily on early diagnosis, prevention of complications and management of internal organ damage. Although haematopoietic stem cell transplantation was found to be an effective treatment method, it is rarely used due to high costs and low human leukocyte antigen (HLA) compatibility [6, 7]. SCD is inherited in an autosomal recessive pattern (it is not a sex-linked trait) with the co-dominant allele. This means that carriers of a single copy of a mutant HbAS gene do not normally present with clinical symptoms, but they do have erythrocytes which contain around 40% HbS [8]. Homozygous patients with HbSS usually live shorter due to vascular occlusion and subsequent organ damage.

According to the WHO there is an urgent need to establish sickle cell anaemia control programmes in Africa, where the mortality of children due to SCD ranges from 50 to 90%. In most developed countries, newborn screening programmes have effectively reduced early childhood SCD mortality. However, implementing similar programmes in developing African countries would be very difficult due to logistic and economic reasons [9, 10]. WHO has recognized SCD as a global public health concern. Tanzania is one of the countries with the highest birth prevalence of SCD. The available literature on SCD morbidity in Tanzania focuses primarily on the residents of the mainland [11–15], while there is little data available on SCD morbidity among residents of the Tanzanian islands in the Indian Ocean. The aim of the present study was to confirm the presence of sickle cell disease among residents of the Zanzibar Archipelago.

MATERIAL AND METHODS

The study was conducted on Pemba Island, the second largest island of the Zanzibar Archipelago, which has a total area of 1014 km^2 (the name of the largest island of the Archipelago is Unguja, but it is commonly referred to as Zanzibar) (Fig. 1).

Pemba Island is located 50 km west of the mainland Tanzania. It is inhabited by over 400,000 people, of whom more than 90% are Muslims. The population density is 428 people per 1 square km, and the annual population growth is estimated at 3.1% [16]. Chake Chake, inhabited by 52,000 people, is the island's largest town and administrative centre. There are two hospitals in the town: a state-run District Hospital and a privately owned Amal Hospital.

The study group consisted of 27 people whose at least one parent has sickle cell anaemia. All patients provided informed consent to participate in the study. For paediatric patients, informed consent was obtained from the children's parents or legal guardians. The study was performed at the Amal Hospital (Chake Chake Town, Pemba Island) in June 2023. Blood samples collected from the study participants were tested using HemoTypeSC™, a rapid, point-of-care diagnostic test.

METHOD DESCRIPTION

HemoTypeSC™ is a rapid test kit for the determination of haemoglobin type, which incorporates monoclonal antibodies for the detection of haemoglobin A, S, and C in whole blood or capillary blood samples. The assay pro-

Figure 1. Map of the Zanzibar Archipelago

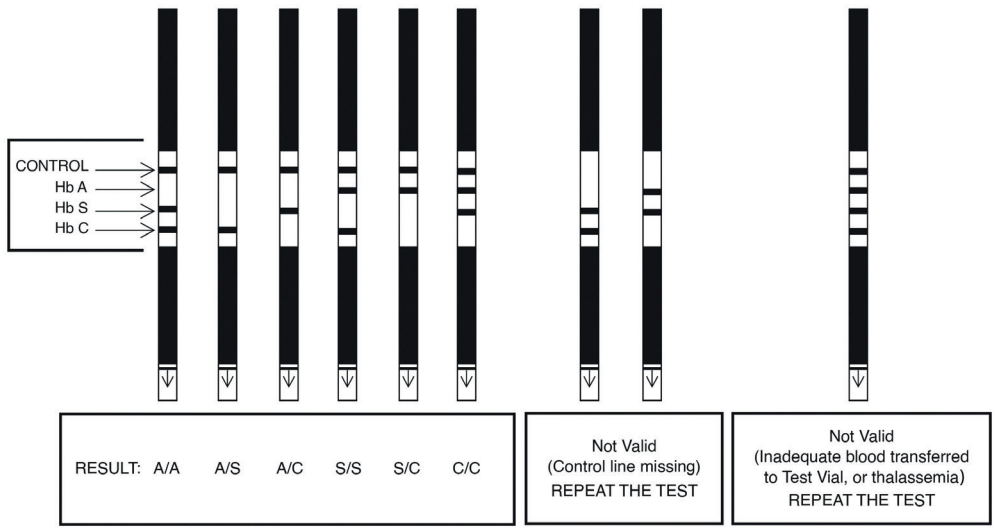

Figure 2. The result chart of HemoTypeSC™ for reference

vides determination of haemoglobin phenotypes HbAA, HbSS and HbSC, HbCC, HbAS and HbAC. The test kit includes a foil pouch containing: 50 single-use test strips, 50 single-use blood sampling devices, 3 reusable dropper pipettes and instructions for use. The test kit does not provide the following materials: (they must be obtained separately): water, a timer, lancets, test vials (1.5–5 mL), a compatible rack for holding the vials. The test procedure is quick and easy to follow. First, using dropper pipette, add 6 drops of water into a test vial and place the test vial in a compatible rack. Use a lancet to prick the skin to obtain a blood sample (1 to 2 microliters). Touch the white pad of the blood sampling device to a blood droplet, make sure the white pad absorbs the blood droplet and the whole white pad has turned red. Insert blood sampling device into a test vial filled with water and swirl gently to mix. Ensure that water has become pink or light red. Next, insert a test strip into the test vial (without removing the blood sampling device) and wait for 10 minutes. After 10 minutes, take the test strip out of the vial and read the result (Fig. 2).

ETHICAL CONSIDERATIONS

Ethical clearance for conducting health research in the Zanzibar Archipelago was obtained from the Zanzibar Health Research Ethical Committee Secretariat of the Zanzibar Health Research Institute on 8 June 2021 (Ref. No. ZAHREC/03/REC/June/2021/12).

RESULTS

Blood tests were performed on a group of 27 individuals aged between 2 months and 26 years old, whose at least one parent had sickle cell anaemia. Homozygous HbSS phenotype (confirmed SCD) was found in 11 study subjects (40.7%); their haemoglobin concentration was between 6.6–8.5 g/dL. Heterozygous HbAS phenotype (confirmed carriage or trait) was found in 14 participants (51.9%). Only 2 individuals (7.4%) had normal HbAA haemoglobin phenotype (Table 1), they were: an 8-year-old girl and a 16-year-old girl, whose haemoglobin concentration was 12.1 and 11.8 g/dL, respectively. In a group of children under 1 year of age we found 2 cases of HbSS (indicating sickle cell disease) and 7 cases of HbAS (trait/carriage). In the group of children aged 2–13 years old there were 6 cases of HbSS and 6 cases of HbAS. In the group of patients > 13 years old we found 3 cases of HbSS and 1 case of HbAS. All patients who have been diagnosed with sickle cell disease had haemoglobin concentration below 8.5 g/dL (mean: 7.34 g/dL). Low haemoglobin concentration was also observed in HbS carriers. Apart from 4 cases, the mean haemoglobin concentration in patients with HbAS was higher than in patients with confirmed SCD (mean: 9.6 g/dL).

Table 1. Sickle cell disease test results in patients tested at the Amal Hospital, Pemba, the Republic of Tanzania, June 2023 (n = 27)

No.	Sex	Age [years]	Hb [g/dL]	Norm (HbAA)	Sickle cell (HbSS)	Carrier (HbAS)
1	M	9	13.3			x
2	F	8	12.1	x		
3	M	8	7.2		x	
4	F	8 months	8.9			x
5	M	6	7.4		x	
6	F	2	6.7		x	
7	M	9 months	6.9		x	
8	F	16	11.8	x		
9	M	20	6.8		x	
10	F	19	12.2			x
11	M	8 months	9.1			x
12	M	4	6.6		x	
13	F	2	11.5			x
14	F	7 months	7.1		x	
15	F	26	8.5		x	
16	M	9	11.4			x
17	F	10 months	7.1			x
18	F	7	8.4		x	
19	F	13	8.1		x	
20	F	11	7.0		x	
21	M	7 months	9.0			x
22	F	4	8.2			x
23	F	3	11.1			x
24	M	1	9.6			x
25	F	2 months	7.3			x
26	M	6 months	9.1			x
27	M	4 months	6.4			x

DISCUSSION

The Republic of Tanzania ranks fifth in the world for the highest number of children born with sickle cell disease. After WHO recognized SCD as a major public health concern in Africa, Tanzania has implemented a series of measures aimed at controlling the disease, including the introduction of educational programmes for healthcare practitioners, increasing testing coverage and establishing specialist medical centres for SCD diagnosis and management. In 2004, Tanzania established the Muhimbili Sickle Cell programme (MSC) which integrated the medical research and management of SCD cases at a national referral hospital (the Muhimbili National Hospital). However, the country failed to introduce a nationwide newborn screening program for sickle cell disease. As a result, there are no official reports on SCD morbidity in Tanzania except for a few studies conducted by local research institutes [17–19]. High costs of the tests currently in use for the diagnosis of SCD and the absence of rapid screening methods remain the two major obstacles in expanding the newborn screening programme for SCD as part of a healthcare intervention in Tanzania.

Christopher et al. [11] carried out a study to determine the diagnostic accuracy of the HemoTypeSC™ point-of-care SCD test. They found that the test had 100% sensitivity

and specificity for detecting HbSS, HbAS and HbAA haemoglobin phenotypes. Other studies into the same subject have shown similar findings [20, 21], but some researchers pointed out that the test's sensitivity and specificity was higher in adults than in newborns (99.8% and 99.9% in adults; 98.1% and 99.1% in newborns, respectively) and that the test's sensitivity and specificity was even lower (98.2% and 99.7%, respectively) when cases of thalassaemia S/β0 and thalassaemia S/β+ were included in the analysis. Despite its limitations, HemoTypeSC™ test is considered a reliable, quick, and cost-effective diagnostic tool for an early diagnosis of sickle cell anaemia and is recommended for population-based screening in high-risk areas such as Tanzania.

The present study involved residents of Pemba Island in the Zanzibar Archipelago, which is part of the Republic of Tanzania. Previous studies into SCD morbidity in Tanzania by local or international researchers were usually carried out in Tanzania Mainland. There is little data available on SCD morbidity among residents of the Zanzibar Archipelago, although the total population of the archipelago (Zanzibar, Pemba and Mafia islands) is estimated at 2 million people. The present study, which was conducted at the Amal Hospital in Chake Chake town on Pemba Island, focused on a specific group of patients, i.e. patients whose at least one parent had sickle cell anaemia. On top of testing the patients included in the study, we also tested their close relatives; this was done to assess the scale of the spread of the mutant HbS haemoglobin among family members. We found that of 27 individuals involved in the study only two had normal haemoglobin phenotype (HbAA), whereas 11 study subjects (64% of whom were children under the age of 8 years old) had HbSS phenotype. Much of the available data on the survival of children with HbSS suggest that most children diagnosed with SCD die in early childhood, which might explain a lower prevalence of HbSS phenotype among older children and adults [19]. The present study found a correlation between the age of study participants and the prevalence of HbSS haemoglobin. However, the results are limited by a small sample size and difficulties associated with the assessment of survival rates. It is estimated that infant mortality in Tanzania ranges between 70 and 80 per 1,000 live births. An estimated 230,000 children under the age of 5 years old die in Tanzania each year; 14,700 of these deaths are related to sickle cell disease. The mortality rates in Tanzania vary depending on the region (mortality rates are usually lower in bigger cities or towns, where people have better access to healthcare and a higher socio-economic status, and higher in rural areas) [12, 16].

In general, researchers are of an opinion that it is possible to reduce elevated mortality due to SCD among children under the age of 5 years old. In South America, the prevalence of sickle cell disease has been significantly reduced through a series of simple interventions, such as early diagnosis (newborn screening programmes) and the introduction of comprehensive healthcare programmes for SCD-affected patients (infection prevention, early diagnosis, management of complications). These interventions improved the survival of children with SCD by 50%. Moreover, the South American programme showed that health education itself (e.g. raising awareness of how to manage febrile illnesses and splenic sequestration) can effectively reduce SCD mortality in young children [19, 22]. Due to Tanzania's economic status (the World Bank has classified it as a low-middle-income country), implementing similar intervention programmes would be very difficult for economic and logistic reasons.

Ambrose et al. [14] developed a novel method for the diagnosis of sickle cell anaemia which is based on the existing infrastructure used to detect HIV infections among infants. They found that the dry blood spot technique (in which a few drops of a blood sample are applied onto specially manufactured membrane filters and then transported to a reference laboratory) used for early infant diagnosis of HIV can also be used for the detection of SCD cases. The same researchers pointed out that the use of HemoTypeSC™ test, which has been proven to be reliable and cost-effective, can greatly reduce the costs of large-scale screening for SCD. Their study (which used the dry blood spot technique and the infrastructure for diagnosing HIV infections in infants) showed that the prevalence of sickle cell trait (HbAS) and sickle cell disease (HbSS) in Tanzania was 20% and 1.5%, respectively [14, 17]. Another study into the same subject involved a group of children under the age of 5 years old living in Southern Tanzania. The primary inclusion criterion in this study was haemoglobin concentration below 10 g/dL. The study found that 18% of the participants (n = 50) had sickle cell anaemia and that the mean haemoglobin concentration among study subjects was 6.4 g/dL [15].

The results of the present study were limited by a small sample size and its specific composition. Therefore, they cannot be considered representative for the general population of Pemba Island and do not reflect the actual morbidity rates of sickle cell anaemia among Pemba residents. However, the results of the present study suggest that sickle cell anaemia is likely to spread rapidly across the region due to high rates of consanguineous marriages and tribal endogamy (most of the people living in the Zanzibar Archipelago are Muslims) [23].

CONCLUSIONS

According to the World Health Organization, there is an urgent need to establish sickle cell anaemia control programmes and regular screening of newborns and infants in Africa. The results of the present study support the necessity to introduce population-based screening for SCD in the Zanzibar

Archipelago, especially in infants whose family members have a history of sickle cell disease. Such interventions will help monitor the number of new SCD cases in the region and may potentially reduce infant mortality as well as minimize negative effects of SCD in older children through the adoption of effective disease prevention measures.

ARTICLE INFORMATION AND DECLARATIONS

Data availability statement: The authors confirm that the data supporting the findings of this study are available within the article.

Ethics statement: Ethical clearance for conducting health research in the Zanzibar Archipelago was obtained from the Zanzibar Health Research Ethical Committee Secretariat of the Zanzibar Health Research Institute on 8 June 2021 (Ref. No. ZAHREC/03/REC/June/2021/12).

Author contributions: Wanesa Richert — preparation of the project and typescript; Mohammad Othman Atumani — diagnostics; Daria Kołodziej — selection of the data; Krzysztof Korzeniewski — selection of the data.

Funding: No funding.

Acknowledgments: No acknowledgments.

Conflict of interest: Authors declare no conflict of interest in relation to this article.

Supplementary material: No supplementary material.

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