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Association between Hepatic Enzymes Levels and Persistent Hepatomegaly in Sickle Cell Patients

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Abstract

Background

Sickle cell disease is one of group of blood disorders and diseases that affect red blood cells. Like other haemoglobinopathies, sickle cell disease is inherited single-gene disorders inherited as autosomal co-dominant traits characterized by a single point mutation in the β-chain of human haemoglobin leading to life-long illness. The severity of the disease varies widely from person to person essentially due to resultant multi-organ failure including liver dysfunction, which can be multifactorial.

Broad Objective

This study, was carried out to determine the association and potential role hepatic enzymes as biochemical indices may have on the severity of sickle cell anaemia diseases.

Methods

This was cross-sectional study that was done at sickle cell clinic at Muhimbili National Hospital in Dar es Salaam, Tanzania using an English checklist as a main research tool with a sample size of 75 eligible sickle cell patients. All sickle cell patients who had been attending clinic from September 2016 to October 2016 and had hepatic enzymes test being done were included in the study. Categorical variables were compared using Chi-Square (χ^2) and binary variables tested using Cochran–Mantel–Haenszel test with p-values <0.05 considered statistically significant. The main findings show that, there was significant association between hepatomegally and liver function tests in patients with sickle cell disease. The association between hepatomegaly and abnormalities in all liver function tests, including alanine transaminase (ALT), aspartate transaminase (AST), bilirubin, albumin and total protein levels was statistically significant ($p < 0.05$). The Cochran–Mantel–Haenszel test (CMH) for binary categorical variables as well as the association between liver function tests abnormalities and hepatomegaly had exact match ($p = 0.05$).

Conclusion

This study found association between abnormalities in liver function tests and hepatomegaly in sickle cell patients to advocate regular screening as an urgent remedy to prevent adverse lethal complications in African setting.

Key Words: *Hepatic Enzymes, Hepatomegaly, Sickle Cell Disease.*

Introduction

Cells in tissues need a steady supply of oxygen to maintain the functionality. In principle, haemoglobin is the means that red blood cells take up oxygen in the lungs and carries it and deliver oxygen (O_2) to all body tissues of the via blood flow through the circulatory system (1). Normal red blood cells containing normal haemoglobin will usually look disc shaped (like a doughnut without a hole). This shape allows flexibility of the cells for smooth movement through large and small blood vessels to various tissues and organs where they deliver oxygen. In so doing, the blood flows to supply tissues and organs with nutrients.

Oxygen-deprived tissues can result into sudden heart attacks and severe pain, commonly called pain crises. As these sudden and painful attacks occur without warning, a person will often need to go to the hospital for immediate and effective attention. Abnormal red blood cells, commonly known as sickle cells are common haemoglobinopathies that can lead to red cell functional impairment. Such condition is termed, sickle cell disease (SCD) and is among group of blood disorders and diseases that affect red blood cells. Like other haemoglobinopathies, sickle cell disease is an inherited autosomal co-dominant single-gene trait disorders characterized by a single point mutation in the β-chain of human haemoglobin (2). As such, sickle cell disease can result into biochemical abnormalities leading to life-long illness (3). The severity of the disease varies widely from person to person essentially due to resultant multi-organ failure including liver dysfunction, which can be multifactorial (4, 5). Most children with sickle cell disease (SCD) are pain-free between painful crises, but adolescents and adults may also suffer chronic ongoing pain because the rate of cells production is higher in children than in adults since they are still growing and therefore children have adequate supply of oxygen (6).

In sub-Saharan Africa, epidemiological data indicate the highest incidence of sickle cell anaemia with severest and often fatal forms concentrating in children under the age of 5 years (7). Greater severity in Africa is exacerbated by a combination of factors that may include coexistence with Plasmodium falciparum malaria as well as unfavorable demographic setting that involve endogamy, poor healthcare facilities, and poor socio-economic conditions (8). During childhood, the most common non-communicable diseases are haemoglobinopathies with SCD being the commonest contributing to childhood mortalities. In Tanzania, about 10,313 children are estimated to die every year before the

age of 5 years due to with SCD contributing an estimated 7% of overall deaths in children aged less than 5 years old, despite the claimed overall reduction in childhood mortality in the country (9).

In sickle cell anaemia finding hepatomegaly is not unexpected finding and when persists has frequently been associated with increased severity of the disease. It is known that the liver involvement in disease severity commonly occurs independent of spleen status and may not be associated with the overall acute severe episode (10). In sickle cell both hepatomegaly and splenomegaly associated with disease vary in size which could imply a severe clinical course of the disease (11) and are related to a decrease in hematocrit (12). Persistent hepatomegaly in particular, is reported to be indicative of severe clinical course [13], worse enough, splenomegaly may persist beyond childhood (14) and may be lethal if combined with elevated liver enzymes are elevated; plasma bilirubin concentrations, and aspartate aminotransferase (15). With advancement in diagnostic facilities like utrasonography, it is now possible to compare hepatomegaly with splenomegaly, cholelithiasis (16) and their association with biochemical tests to get a clear picture in such patients (17) which is important in planning for disease management.

Various clinical and hematological indices have been used to assess the severity of Sickle Cell Anaemia (SCA), however a focus on biochemical indices and their association with severity of the disease in hepatomegaly patients is lacking. The rationale of this study was to use laboratory liver function tests in the evaluation of hepatic dysfunction and splenomegaly as a consequence of sickle cell disease. Our study used patient information in records to find associations of culminating measurements including liver functions tests to evaluate their associations in sickle cell disease with and without splenomegaly indicative of consequences of the disease on various organ functions. The aim was to generate information that could create a base for additional index that can be used to assess the severity of sickle cell anaemia besides clinical and haematological indices. The study assessed clinical and hematological indices for severity in sickle cell anaemia patients with and without persistent hepatomegaly as well as levels of liver enzymes (AST, ALT, PT), protein albumin and total proteins in patients with and without persistent hepatomegaly and their association.

Patients, Materials and Methods

This was a cross-sectional study design in which, data were collected from hospital records at a sickle cell clinic in Muhimbili National Hospital (MNH). The study also included analytical work to establish some associations between variables. MNH is the National Referral and University Teaching Hospital with 1,500 bed facility, attending 1,000 to 1,200 outpatients per week, and admitting 1,000 to 1,200 inpatients per week. The hospital has two clinics a week for Sickle Cell Disease patients, one for children, attending an average of 60 patients (on Thursdays) and the other for adults, attending an average of 80 patients (on Fridays). It is the major referral hospital in Tanzania located in the Eastern zone of Tanzania in Dar es Salaam city. The study included sickle cell patients who had been attending clinic from September to October 2016. A criterion was set such that all patients that attended sickle cell clinic and had hepatic enzymes test done were included in the study. The study though, excluded all sickle cell patients who did not test for hepatic enzymes levels. As such, a total of 105 patients were included in the study and their data are presented in this paper.

Data collection tools

A checklist was prepared for data collection and it included social and demographic information, clinical and haematology indices and hepatic level sections. Complete patient's history was taken with all other parameters for clinical severity like number of transfusions and number of crises and symptoms of liver involvement recorded. As per procedure, a thorough general and systemic examination focusing mostly on gastrointestinal system was done. For hepatomegaly, patients with palpable liver margin 10 cm below the right coastal margin were considered to have hepatomegaly and those with hepatomegaly for 6 months or more were considered persistent. Blood was then drawn for complete blood count (to look for haemoglobin levels) and liver function tests. Liver function test results for those patients who tested in the past 3 months were referred prior to data collection. Patients whose liver function test results were not yet available were asked to test and results recorded for subsequent evaluation.

Sampling methods and strategy

Convenience sampling technique was used in selecting patient records for this research until when, the collected data were sufficient to provide meaningful findings. The outcome of

interest assessed in this study was obtained from each individual who was enrolled and thus the data were collected from hospital records.

Variables

Anthropometric variables such as age, sex, level of education, socioeconomic status of individual and occupation were sought in an attempt to gather as much information as possible to complement what was obtained from clinical data of the patient. Dependent variables were mainly hepatomegaly, haematological and biochemical indices for severity in sickle cell anaemia obtained from patient's history of disease and from the patient's hospital records. These records are commonly and widely used in assessment of severity of sickle cell disease in the clinic.

Ethical consideration

Ethical clearance was sought from the MUHAS Senate Research and Publications Committee and to conduct the study at MNH was sought from the MNH responsible authorities. Since the data were collected from hospital records, there was no formal informed consent from study participants whose data was used in this study, but ethical consideration procedure was followed before the beginning, during and after the study in which confidentiality was observed as per research requirements involving human subjects. The study had no risks to patients from whom records were kept, therefore informed consent was not a requirement, and permission from the MNH authorities and ethical clearance from MUHAS ethical approval were sufficient to unable data collection from health records.

Data processing and analysis

The data were entered, cleaned and analysed using a computer-based Statistical Package for Social Sciences (SPSS version 23.0. SPSS Inc., Chicago, IL, USA). Association of variables was tested using relevant measures of associations. Categorical variables namely liver function tests and hepatomegaly were compared using Chi-Square (χ^2) and binary variables such as gender were tested using Cochran–Mantel–Haenszel test with p-values < 0.05 considered statistically significant.

Results

Socio-demographic characteristics

In this study, 30 subjects had missing variables thus it is the remaining 75 sickle cell patients which were evaluated for various parameters (**Table 1**). About half (n=37, 49.3%) of the study patients fell in the age range of 1 – 11 years while 57 (76%) of all study participants were predominantly females. Thirty-one (41.3%) of patients had never been exposed to formal education.

Table 1: Socio-demographic Characteristics of 75 sickle cell patients

Variable	Age group	Frequency	Percent
Age	1 – 11 12 – 22 23 – 33	37 24 14	49.3 32.0 18.7
Sex	Male Female	18 57	24.0 76.0
Level of education	None Primary education Secondary education College/ university	31 24 18 2	41.3 32.0 24.0 2.7

Sickle cell disease and hepatomegaly

In total, 25 (33%) of patients with sickle cell disease had hepatomegaly, which is a considerable proportion of patients to mention. Most of patients 69 (92%) made 1-3 visits to the clinic with few 6 (8%) having more than 3 clinic visits. Blood transfusion was performed in 69 (92%) of patients most of them having highest number of visits to the clinic (**Table 2**). Of these patients, frequency of blood transfusions was highest in those with no hepatomegaly (49, 65.3%). Number of crisis also was related to non-hepatomegaly group (1-3 clinic visits). In this study patients with hepatomegaly were observed to have poor clinical outcome compared to those without.

Haematological parameters

In this study 66 (88%) of the patients had normal levels of PCV out of whom 20 (30%) had hepatomegaly. Twenty-five (33.3%) of all sickle cell patients with hepatomegaly had reduced levels of haemoglobin, and 17 (68%) of patients with hepatomegaly had normal levels of platelets as well as normal MCV (**Table 3**). About 24 (32%) patients with and without

hepatomegaly had elevated levels of WBC since they were admitted primarily due to other varying sorts of infections.

Table 2: Clinical features of 75 sickle cell disease patients both in relation to hepatomegaly status

		Hepatomegaly		
		Yes* n=25	**No n=50**	**Total**
No. of visits	1-3 More than 3	21 04	48 02	69 06
No. of Blood Transfusion	1-3 More than 3	20 05	49 01	69 06
No. of Crises	1-3 More than 3	19 06	46 04	65 10

**Patients with hepatomegaly had poor clinical outcome compared to those without as picked from the records.*

Table 3: Hematological results of sickle cell disease patients in relation to hepatomegaly

		Hepatomegally		
		Yes	**No**	**Total**
PCV	Elevated Normal Reduced	00 20 5	1 46 3	1 66 8
WBC	Elevated Normal Reduced	24 1 0	33 16 1	57 17 1
HB	Normal Low	0 25	1 49	1 74
Platelets	High Normal Low	0 17 8	3 36 19	3 53 19
MCV	Elevated Normal Reduced	1 17 8	2 38 10	2 55 18

Patients with hepatomegaly had poor hematological results compared to those who didn't have hepatomegaly particularly WBC and PCV ($p<0.05$).

Hepatomegaly and liver function tests

This study assessed the association between liver function tests and hepatomegaly and 22 (29%) out of 75 patients had hepatomegaly of whom 20 (90%) had elevated AST and ALT levels, the elevation being significant statistically ($p < 0.001$). The results also showed that 21 patients out of 22 (95%) had statistically significant elevated levels of bilirubin and albumin ($p< 0.001$). Most of the patients without hepatomegaly had normal levels of liver function tests (**Table 4**).

Table 4: Association between hepatomegaly and liver function tests in 75 patients with sickle cell disease.

		Hepatomegaly			
		Yes n=25	**No n=50**	**Total**	**p-value**
AST	Elevated Normal	22 03	0 50	22 53	<0.001
ALT	Elevated Normal	22 03	0 50	22 53	<0.001
Bilirubin	Elevated Normal	21 04	0 50	25 50	<0.001
Albumin	Elevated Normal	21 04	0 50	21 54	<0.001
Total Protein	Elevated Normal	21 04	0 50	21 54	<0.001

Discussion

General characteristics of a population, such as age, gender, ethnicity, education level, income, type of client, years of experience and location were assessed in this study. Our findings from assessment of association between hepatic enzymes level and persistent hepatomegaly in sickle cell patients revealed a number of relationships in parameters that could have impact on life of this group of patients. Studies have reported a wide range of clinical spectrum of SCD from mild liver function test abnormalities to significant hepatic abnormalities with marked hyperbilirubinemia [18, 19]. In our study, a total of 75 sickle cell patients were evaluated for various parameters, the study found nearly half (37, 49.3%) of the study patients being in their early ages of life (1 – 11 years) with 57 (76%) of all patients' studies being predominantly females. No scientific explanation for the larger proportion of females to males in this study. SCD has no gender predilection due to autosomal recessive

nature of the disorder [20]. Reports on SCD and gender have principally indicated no gender predilection despite highlighting gender differences in pain crisis where male are more prone (20). Other gender-biased differences have been on increased anxiety linked to pregnancy (21), variable hypertension and sickle cell nephropathy (22). The fact that nearly 50% of studied patients fell in the age range of less than 11 years old, could be the reason for the relatively large group of patients (31), 41.3% who had no formal education attributable to younger age. Most of the patients less than 11 years of age were children aged less than 5 years old, an age that is a year short of school life in Tanzania. The findings however have a reflection that, that sickle cell trait can be detected as early as 3 months of childhood life which is necessary information for early screening (23) as part of management to reduce early deaths (24) due to early threatening complications (25) particularly in our low-income countries.

The results from this study revealed that most of patients (92%) made 1-3 visits to the clinic with few 6 (8%) having more than 3 clinic visits. The frequency of patient visits clinic is an indication for dedicated adherence to medical attention by these patients. It is through these visits that patients' status can be fully evaluated and remedy made depending on need which are variable. As was shown in the results, blood transfusion was performed in 69 (92%) of all patients most of whom having highest number of visits to the clinic. Sickle cell patients are prone to vaso-occlusive crises which can lead to hypoxemia (26) and can only be relieved through blood transfusion (26, 27). The frequency of blood transfusion was highest in patients with no hepatomegaly (49, 65.3%) who too, had hypoxia crises, especially those with 1 – 3 clinic visits. This could be due to complicity of sickle cell hepatopathy whose different types of syndromes sometimes are difficult to distinguishing (28) including other unnoticed complications (29). Patients with hepatomegaly were observed to have poor clinical outcome compared to those without. This is because presence of hepatomegaly in sickle cell patients can lead to injury of the liver an abnormality that together with splenomegaly, intrahepatic cholestasis and cholelithiasis have been implicated to result into poor clinical outcome (30).

The study found larger proportion 66 (88%) of the patients with normal levels of PCV of whom 20 (30%) had hepatomegaly. Nevertheless, all 25 (100%) of the patients with hepatomegaly had reduced levels of haemoglobin because of the infections and acute bone marrow suppression. In sickle cell associated hepatomegaly, there is possibility of

development of aplastic anaemia characterized by pancytopenia and hypocellular bone marrow which might have been responsible for observed haemoglobin levels [29]. The results also revealed that 17 (68%) of patients with hepatomegaly had normal levels of platelets as well as MCV compared to (24, 96%) patients with and without hepatomegaly had elevated levels of WBC. This could be due to the fact that these patients were apart from sickle cell disease, admitted due to other infections which are said to result into hepatosplenomegaly and pancytopenia (31). In such patients' reticulocytes (immature RBC with nucleus) are identified as white cells thus its elevation in sickle cell patients (32).

The results from liver function tests revealed strong association with hepatomegaly. The results showed that 22 sickle cell patients with hepatomegaly, 20 (90%) had elevated AST levels and ALT levels and the statistical analysis reflected a significant association ($p<0.001$). In addition, 21 (95%) of hepatomegaly SCD patients had elevated levels of bilirubin and albumin their association with hepatomegaly was statistically significant ($p < 0.001$). The elevation of bilirubin could be due to increased haemolysis of red blood cells due to short life span of sickle red cells compared to normal red blood cells (18, 33, 34) but also could be a result of advanced liver disease (35). However, the use of biochemical surrogates of haemolysis is cautioned as it may not correlate with directly measured haemolysis in some instances (34). Most of the patients without hepatomegaly had normal levels of liver function tests indicating the less proneness to haemoglobinopathies crises than the hepatomegaly ones. In sickle cell disease, there happens a constant haemolysis of red blood cells that result into elevated unconjugated bilirubin and acute liver injury due to vaso-occlusive crises which rises aspartate transaminase (AST) and ALT levels (36). Previous reports are available explaining the elevation of liver enzymes in such patients and that both the plasma bilirubin and aspartate aminotransferase concentrations are all elevated in all the patients with hepatomegaly (15).

Conclusion

Liver function test are useful markers in detection of severity of sickle cell anaemia in patients with persistent hepatomegaly due to its direct reflection of injury to the liver in sickle cell disease. Since sickle cell patients do not normally present with hepatomegaly in steady state, hepatomegaly found in some patients in this study is indicative of unsteady steady making them prone to other worse complications like stroke, splenic sequestration and acute

chest syndrome. The high association between abnormalities of liver function tests and other biochemical indices with hepatomegaly in sickle cell patients calls for routine screening as an urgent remedy to prevent adverse lethal complications and ease prognosis in sickle cell patients.

Limitation of the study

Insufficient funds to trigger investigations that are not routinely done in the hospital that might help to track the magnitude of the problem. Lack of sufficient and important past records for many patients particularly those with longer than 6 months' persistence of hepatomegaly for more detailed information.

Authors' Contribution

RB conceived the study, collected data, performed data analysis and interpretation and drafted the manuscript. EVM conceived of the study, participated in its design and coordinated and helped to draft the manuscript and in revising it critically for important intellectual content, before submission. Both authors approved the final draft and agreed of its content before submission.

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List of Abbreviations

ALT	Alanine Transaminase
AST	Aspartate Transaminase
CMH	Cochran-Mantel-Haenszel
SCD	Sickle Cell Disease
SCA	Sickle Cell Anaemia
MNH	Muhimbili National Hospital
MUHAS	Muhimbili University of Health and Allied Sciences
SPSS	Statistical Package for Social Sciences
WBC	White Blood Cells

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