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Research Article

Misdiagnosis of Sickle Cell Trait contributes to increased burden of Sickle Cell Disease in Sub-Saharan Africa

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Abstract

Background: Sickle cell trait is a heterozygous non-disease condition in which an individual inherits sickle haemoglobin (HbS) with normal haemoglobin A (HbA). Despite increased awareness and testing in Nigeria, it has been observed that the prevalence of sickle cell disease is not decreasing. The aim of the study was to document the burden of misdiagnosis of sickle cell trait in a sample from the most populous country in Sub-Saharan Africa.

Methods: A cross-sectional study of 264 biologic parents of children with sickle cell disease accessing haematology services between January 2019 and December 2019.

Results: The mean ages were 44.2 ± 7.4 years and 37.7 ± 6.4 years for males and females respectively with most having tertiary education. One hundred and forty-four (54.5%) biologic parents of children with sickle cell anaemia had premarital haemoglobin genotype testing done for both parents at least. The prevalence of misdiagnosis was 28.4% and 17.8% in fathers and mothers respectively; 6.7% and 12.7% of fathers and mothers respectively were misdiagnosed twice. Of the children of respondents with sickle cell anaemia, 19.0% were misdiagnosed at least once during genotype testing. Privately owned laboratories and laboratories in private hospitals were identified as the most common facilities for genotype testing (33.3 – 51.1% and 33.3 – 34.8% respectively) and gave the highest rates of misdiagnoses (up to 43.0% and 31.9% respectively).

Conclusion: A national policy is needed to regulate the framework of laboratory testing in Sub-Saharan countries to improve the awareness generated and reduce the scourge of misdiagnosis.

Key words: black women; depression; somatic symptoms; cultural competence; mental health; systemic barriers; community support; holistic health; misdiagnosis; healthcare access

Introduction

Sickle cell trait is a heterozygous non-disease condition in which an individual inherits sickle haemoglobin (HbS) with normal haemoglobin A (HbA). The sickle haemoglobin results from the substitution of the amino acid valine for the amino acid glutamic acid at the sixth position of the β-globin chain of the haemoglobin.[1] Affected individuals do not manifest with symptoms or complications of sickle cell disease except in unusual or extreme conditions like severe dehydration in athletes or hypoxia in high altitude.[2] Generally, individuals with sickle cell trait have a normal life expectancy.

The sickle cell gene is seen predominantly in Africans but can also affect people of other races like Hispanics, Asians, and Caucasians. Globally, more than 100 million people have the sickle cell trait.[2] In Africa, the prevalence of the sickle cell trait varies in different countries, and in these countries, prevalence varies amongst different geographic locations. An important variable is Plasmodium falciparum malaria endemicity which has a direct relationship with the sickle cell gene.[3] The highest prevalence in Africa and probably worldwide was found in the Bundibugyo district of Western Uganda with a rate of 45%,[4] though a more recent study found a prevalence of 13.4%.[5] In Nigeria, which is the most populous country in Africa, the prevalence of the sickle cell trait ranges from 24 – 25%.[6] This is similar to Benin with a prevalence rate of 25%, [7] as both countries have a similar climate and are holoendemic for malaria.

The most common form of sickle cell disease in Sub-Saharan Africa is the homozygous haemoglobin S gene.[8] Sickle cell disease affects up to 3% of

births in some parts of Africa.[8] About 200, 000 newborns with sickle cell anaemia are delivered yearly in Africa [9] and this constitutes approximately 66.6% of the children born with haemoglobinopathies worldwide.[5]

Sickle cell anaemia is a multi-organ disease associated with high morbidity and mortality with the attendant health burden comparable to that of communicable diseases. [10,11] It is estimated that 50 – 80% of children with sickle cell anaemia in Africa will die before their fifth birthday.[12]

Various laboratory diagnostic methods have been developed to promote early diagnosis of sickle cell trait and disease from the fetal to the newborn period, and also for the screening of older children and adults. These tests demonstrate the presence of haemoglobin S, significant reductions in haemoglobin A and variations in the percentages of hemoglobin F and A2 in red blood cells. The screening tests commonly used in Africa are sickling test using sodium metabisulphite and sickle solubility test. The confirmatory tests are hemoglobin electrophoresis (HBE), isoelectric focusing (IEF) and high-performance liquid chromatography (HPLC).[1] These tests are very specific and are used to confirm the sickle phenotype (AS/SS/SC/Sβ-thalassaemia). In addition, HPLC can quantify hemoglobin fractions.

In Africa, the predominant screening method is sickling test using sodium metabisulphite which creates a hypoxic environment that deforms the red blood cells containing haemoglobin S. Confirmatory testing, though mandatory, is not done in many parts of Sub-Saharan Africa because of cost and the weak support infrastructure. In developed countries, HPLC is the predominant diagnostic method.[1]

In Nigeria, there are many laboratories and most, if not all, do hemoglobin genotype testing. The laboratories range from privately owned to laboratories that are part of a primary, secondary, or tertiary health institution. Most adults in Nigeria go for premarital genotype testing on account of the increasing awareness of sickle cell disease and its complications. This is to prevent the couple from having children with sickle cell anaemia and the attendant physical, emotional, psychosocial, and financial burden. Despite the increased awareness and testing, it has been observed that the prevalence of the disease is not decreasing. [13, 14] This study, therefore, aimed to document the burden of misdiagnosis of sickle cell trait in one of the largest tertiary health institutions in Nigeria, and identify which groups of laboratories were associated with the misdiagnosis of the sickle cell trait.

Methods

The study was conducted at the Lagos University Teaching Hospital (LUTH), Lagos State, Nigeria. Lagos State is in the South-Western part of Nigeria and is the center of commerce in the country. The population as of 2016 was estimated to be over 21 million. [15]

The study was cross-sectional in design. The study population included the biologic parents of children with sickle cell disease attending the Pediatric Hematology Clinic and those admitted into the pediatric wards between January 2019 and December 2019.

Ethical approval was obtained from the Health Research Ethics Committee of LUTH prior to the commencement of the study. Informed consent was obtained from the parent of each child after thoroughly explaining the scope, nature, and objectives of the study. Interviewer-administered questionnaires were used to collect the information from each consecutive parent that consented to participate in the study.

The minimum sample size was determined using the formula;

$$n = \frac{z^2 pq}{d^2}$$

Where n = sample size

p = expected proportion of misdiagnosis in the population, assumed to be 20%

q = 1-p

z = standard normal distribution at α level of 0.05 = 1.96 at 95% confidence interval

Sample size, $n = \frac{1.962 \times 0.2\ (0.8)}{0.052}$

$= \frac{3.8416 \times 0.16}{0.0025}$

$= 245.8 \sim 246$

Using a 5% attrition rate (12.3) to make up for incomplete data, total sample size was:

n = 246 + 12.3 = 258.3; this was rounded up to 264.

Therefore, a total number of 264 biological parents were recruited into the study.

Data collected was analyzed using the Statistical Package for Social Sciences (SPSS) software (version 20.0). Results were presented in frequency tables, graphs, and figures. Proportions were used to summarize categorical variables. Pattern of misdiagnosis in each type of laboratory was calculated as the number of misdiagnoses in that center divided by the number of hemoglobin genotype testing done in the center. Level of significance was set at a P value of <0.05.

Results

A total of two hundred and sixty-four biological parents of children with sickle cell disease were included in the study. The mean age of fathers and mothers was 44.2 ± 7.4 years and 37.7 ± 6.4 years respectively [Table 1]. Majority of the parents (62.9% and 59.1% of fathers and mothers respectively) had at least tertiary level of education and were professionals [Table 1].

Among the biologic parents of children with sickle cell anaemia, 144 (54.5%) had premarital haemoglobin genotype testing done for both parents at least once.

The prevalence of misdiagnosis was 28.4% and 17.8% in fathers and mothers respectively; 6.7% and 12.7% of fathers and mothers respectively were misdiagnosed twice [Table 2]. Of the children of respondents with sickle cell anaemia, 19.0% were misdiagnosed at least once during genotype testing [Table 2].

Privately owned laboratories and laboratories in private hospitals gave the highest rates of misdiagnoses (up to 43.0% and 31.9% respectively) [Table 3].

Discussion

The global burden of sickle cell anemia is still largely borne by countries in Sub-Saharan Africa.[14] Currently, Nigeria alone harbors about one-third of all cases of sickle cell disease.[16] Over the years, several studies have proposed different factors responsible for the continued endemicity of sickle cell disease in Sub-Saharan Africa.[16] Worldwide, innovations and breakthroughs in the field of hemopoietic stem cell transplantation have resulted in creation of a definitive cure for the disease, while several interventions such as prophylactic antimalarial and antibiotics administration, newborn screening, transcranial doppler screening and exchange blood transfusions have resulted in increased life expectancy of those with sickle cell anaemia. However, a lot of these interventions are not readily available in resource-constrained settings.[17] Since the goal of eradicating the disease is careful haemoglobin selection by pairing of genotypically compatible pairs, every potential parent with sickle cell trait misdiagnosed as being free of the sickle gene can result in dire consequences.

Previously in Nigeria, poor knowledge and attitude towards premarital hemoglobin genotype testing and counseling resulted in couples giving birth

to children with sickle cell anaemia and a resulting high prevalence of the disorder. This was corroborated in 2015 by Adewoyin et al, [18] in Benin City in Southern Nigeria, who reported that the prevalence of premarital genotype testing was 13.2% and although 98.4% of the respondents knew that sickle cell anaemia was a disease, only 17.8% of respondents had good knowledge of the disease. In Jos, North-Central Nigeria, Oyedele et al,[13] recorded improved awareness of premarital genotype screening (50.7%) and actual screening (52.7%). This improved awareness and screening is as a result of several interventions such as community education programs and outreaches with the participation of religious bodies.[13]

Despite this improvement, there has been no steady decline in the prevalence of sickle cell disease in Nigeria. This implies that there are other factors responsible for this inconsistency. Individuals who had premarital hemoglobin genotype testing at least once before marriage and have been deemed genotypically compatible still give birth to children with sickle cell anaemia.

The study found that slightly over half (54.5%) of couples underwent premarital genotype testing and counselling before marriage which was similar to what was reported by Oyedele et al. [13] In spite of this increased awareness, high prevalence rates of misdiagnosis of sickle cell trait in parents of children with sickle cell disease were noted with rates of 28.4% and 17.8% in fathers and mothers respectively. These parents reported misdiagnosis of the genotype at least once with most misdiagnosed as having genotype AA. With the assurance of a compatible genotype, these individuals got married and unexpectedly had children with sickle cell anaemia with the attendant medical, psychosocial, financial and socioeconomic consequences. This finding was similar to another study in Enugu, South-East Nigeria where all the parents sampled had premarital genotype testing, however 39.1% of the couples ended up with children with sickle cell anaemia.[19]

Misdiagnosis of sickle cell trait was highest in private laboratories and lowest in laboratories situated in tertiary hospitals and the National Sickle Cell Foundation. This is not unexpected as these larger facilities have the capacity to install equipment with better accuracy/precision such as high-performance liquid chromatography, and also to employ trained and experienced professionals to work in the laboratories unlike the smaller facilities with limited resources. Furthermore, factors such as on-specificity of experimental assay, inappropriate allele calling, or random assay instability could also have contributed to the disparity in results between the various laboratories. [20,21] Perhaps, the approach to genotype testing in these laboratories including the use of less efficient methods could account for the high disparity rates observed. In many laboratories, genotype testing is done by haemoglobin electrophoresis and although it has a fairly high accuracy rate, it does not compare in sensitivity and specificity to liquid chromatographic methods which are not widely available.[21]

Even in the children with sickle cell disease, treatment was delayed in 19% because they were misdiagnosed as having another genotype which was predominantly haemoglobin AA (63.3%), and in fewer cases haemoglobin AS (34.7%). This shows that this problem is on-going and definitive measures need to be taken if we are to eradicate it. In a review by Sarat et al,[22] involving103 adults with sickle cell disease, there was a delay in diagnosis in 3.9% of adults which was more pronounced in patients with haemoglobin SC in whom the median age at diagnosis was much later (21 years) compared to 5 years for haemoglobin SS. This may significantly impact their quality of life and increase morbidity and mortality.

In this age where there are several methods of prenatal diagnosis and diagnosis within the first 6 months of life, many children in Nigeria with the disease are still diagnosed later in life following several recurrent vaso-occlusive crises. In Enugu, the age of diagnosis of sickle cell disease ranged from 2 months to14.7 years with a median age of 24 months.[23] Only 10.4% were diagnosed before the age of six months and all were diagnosed after they had presented with symptoms and complications.[23]

Conclusion

The study shows that misdiagnosis of sickle cell trait constitutes a significant problem in Sub-Saharan Africa with 28.4% of fathers and 17.8% of mothers of children with sickle cell anaemia affected, and 19% of children with sickle cell anaemia initially misdiagnosed. The results of this study, although conducted in Nigeria, may be generalizable to most countries in Sub-Saharan Africa because of similar sociodemographic and economic characteristics. The major limitation of this study is that we did not explore the methods of haemoglobin genotype testing in the laboratories to identify which one(s) is (are) associated with errors, or other factors which might contribute towards misdiagnosis of sickle cell trait in laboratories. We therefore recommend increased awareness about its prevalence and counselling of potential parents on the need for confirmatory premarital haemoglobin genotype testing to ensure there are no errors, as well as the development of a national algorithm to testing. We further recommend routine quality improvement checks of laboratories to minimize errors.

What is already known

Increased awareness of a disease leads to disease modifying behaviours and reduced prevalence.

What this study adds

Increased awareness does not translate to a reduced burden in the setting of poor regulation of laboratories, absence of national guidelines and poor laboratory quality management systems.

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Declarations

i. Funding: Not applicable

ii.Conflict of interest/Competing interests: None

iii. Ethics approval: Obtained from the Health Research Ethics Committee of LUTH prior to the commencement of the study.

iv. Consent to participate: Obtained from parent(s) prior to administration of the questionnaires.

v. Consent for publication: Respondents were informed that research findings will be published and their consent was obtained prior to administration of the questionnaires.

vi. Availability of data and material (data transparency): Yes

vii. Code availability (software application or custom code): Statistical Package for Social Sciences (SPSS) software (version 20.0)

viii. Authors' contributions:

a. Study Design: JE, AA

b. Literature Search: JE, AJ, FB, AA

c. Data Collection: JE, AJ, FB

d. Data Analysis: AJ, FB, AA

e. Manuscript Preparation, Editing & Review: JE, AJ, FB, AA

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