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Proportional Derangement in Iron Parameters of Sickle Cell Anaemia Subjects in Calabar Nigeria

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Author for Correspondence *: +234-803-677-7296/ecakwiwu@gmail.com**Abstract**

Maintaining iron balance is critical in the management of sickle cell anaemia (SCA). However, iron parameters are not routinely assessed for patients in resource-poor settings. This study assessed iron parameters of SCA subjects in Calabar with a view to determining the proportions of subjects with iron derangements. This study was carried out among consenting steady-state SCA subjects attending the clinic at University of Calabar Teaching Hospital Calabar, Nigeria. Adult male and female sickle cell anaemia subjects aged 18-35 years were consecutively enrolled in the study. Haemoglobin concentration and haematocrit were analyzed by automation. Serum iron and total iron-binding capacity were analyzed by standard colorimetric methods while serum ferritin was assayed by enzyme-linked immunosorbent assay technique. Statistical analysis was performed using Student's t-test and the level of significance was set at $p \leq 0.05$. The haemoglobin concentration, haematocrit and serum iron levels were found to be significantly low whereas serum ferritin and total iron-binding capacity levels were observed to be significantly higher among SCA subjects compared to subjects with normal adult haemoglobin. Anaemia was present among all SCA subjects. High proportions of reduced serum iron and elevated serum ferritin were also observed among these subjects. Among steady state SCA subjects who had not received blood transfusion within the preceding one year, more than 80% of them had regular routine access to conventional healthcare. Anaemia was present among all the enrolled SCA subjects, while

reduced serum iron and elevated serum ferritin proportions were observed.

Key words: Sickle cell anaemia, haemoglobin, serum iron, ferritin

Introduction

Sickle cell anaemia is one of the non-communicable health conditions with global childhood mortality impact, especially among persons of African descent (McGann, 2014; Grosse *et al.*, 2011). Efforts are ongoing with regards to prevention as well as better management of affected persons towards increased life expectancy. Sickle cell anaemia continues to be a health challenge in Nigeria where it occurs mostly due to lack of knowledge on the part of uninformed couples (Akwiwu *et al.*, 2019; Adegoke *et al.*, 2015; Akwiwu *et al.*, 2011). The sickling of red blood cells particularly within the microvasculature gives rise to further disease manifestation including vaso-occlusion, pain and haemolysis (Bennewitz *et al.*, 2017; Modell and Darlison, 2008). These outcomes therefore become the basis for hospital visitation and admission. Consequently, the management of crisis often centers around the alleviation of the immediate presenting symptoms in order to provide some respite to the suffering patient. Routine checkup, as a long-term management approach for sickle cell anaemia subjects, centers on preventing pain episodes, addressing symptoms and managing complications. Unfortunately, health check for affected persons is sometimes hampered by individual socio-economic status of the patients such that those unable to afford the cost of

healthcare end up being less monitored. This is the prevailing situation in most resource-poor settings where healthcare generally suffers from poor funding and inadequate infrastructure. For the underprivileged in these areas, hospital visitation becomes only necessary in times of crisis, thus limiting the gains of timely interventions (Akwiwu *et al.*, 2019; Akinyanju *et al.*, 2005).

One of the sensitive areas in the management of sickle cell anaemia is the maintaining of sufficient number of red cells to support oxygen supply. Haemolytic anaemia which characterizes the disorder poses a serious threat to life no doubt, yet high packed cell volume is also implicated as a mediator of crisis (Akinbami *et al.*, 2012). Another such sensitive aspect is the need to ensure iron balance owing to the deleterious effects of either of the extremes. While iron is thought to be lost through haemolysis, transfusion therapy often necessitated by severe anaemia serves as an avenue for possible iron overload. There are divergent views from previous reports on iron parameters of sickle cell anaemia subjects (Walter *et al.*, 2009; Fung *et al.*, 2008; Fung *et al.*, 2007; Ballas, 2001). However, dissimilar result patterns may rather be indicative of the prevailing disease course within different studied populations. A sensitive approach to determining iron status could be to investigate the proportional derangement of iron parameters among sickle cell anaemia subjects of a defined population.

Materials and Methods

This study was carried out among 40 consenting steady-state sickle cell anaemia subjects attending clinic at University of Calabar Teaching Hospital Calabar, Nigeria. Ethical approval was obtained from the Health Research Ethical Committee of University of Calabar Teaching Hospital, while informed consent was obtained from each participant enrolled in the research and confidentiality was maintained. The sample size for this cross-sectional study was derived from 2% prevalence of SCA in Nigeria (Fleming *et al.*, 1979). Adult male and

female sickle cell anaemia subjects aged between eighteen and thirty-five years were consecutively enrolled in the study. The sickle cell anaemia subjects were recruited from the Haematology Daycare Clinic at the University of Calabar Teaching Hospital, Calabar. Subjects with normal adult haemoglobin (Hb AA) were apparently healthy age and gender-matched residents of same locality who were not on iron supplements at the time of study. Sickle cell anaemia subjects below the age of eighteen years, those in crisis as well as persons who had received blood transfusion within the preceding one year were excluded from the study.

Blood samples were collected into ethylene diamine tetra-acetic acid bottle and plain bottles. Haemoglobin concentration and haematocrit were analyzed by automation using SMART-1 Haematology Analyzer (Kinghawk Technology Co., Ltd, China). Serum iron and TIBC were analyzed by standard colorimetric methods while serum ferritin was assayed using Human Ferritin ELISA kit (BioCheck, Inc South San Francisco, USA). Statistical analysis was performed on Microsoft Excel (MS office 2010) for windows and SPSS version 20.0 The Student's t-test was used in this study. Results are expressed as numbers with percentages and mean \pm standard deviation. The level of significance was set at $p \leq 0.05$.

Results

A high percentage of the enrolled subjects were below 30 years of age. Females constituted majority of the study participants compared to male. Most of the enrolled persons were keeping to routine checkup regularly at the center (Table 1). The haemoglobin concentration, haematocrit and serum iron levels of SCA subjects were found to be significantly lower compared to values from Hb AA controls, while, serum ferritin and total iron-binding capacity levels were observed to be significantly higher among sickle cell anaemia subjects (Table 2). All the sickle cell anaemia subjects were observed to be anaemic. High proportions of reduced serum iron and elevated serum ferritin were also seen (Table 3).

Table 1. Demographic Parameters of the study participants

| Parameter | SCA (Hb SS) Subjects Number (%) | Hb AA Subjects Number (%) |
|----------------------|------------------------------------|------------------------------|
| Age | | |
| 18-23 years | 18 (45.0) | 20 (50.0) |
| 24-29 years | 16 (40.0) | 14 (35.0) |
| 30-35 years | 6 (15.0) | 6 (15.0) |
| Total | 40 (100) | 40 (100) |
| Gender | | |
| Female | 29 (72.5) | 29 (72.5) |
| Male | 11 (27.5) | 11 (27.5) |
| Total | 40 (100) | 40 (100) |
| Routine Check | | |
| Regular | 33 (82.5) | - |
| Irregular | 7 (17.5) | - |
| Total | 40 (100) | - |

Table 2. Iron-related parameters of sickle cell anaemia subjects and Hb AA subjects

| Parameter | SCA (Hb SS) Subjects n = 40 | Hb AA Subjects n= 40 | p-Value |
|-------------------|-----------------------------------|-------------------------|---------|
| Hb g/l | 94.72 ± 11.36 | 144.56 ± 12.31 | 0.001 |
| HCT l/l | 0.26 ± 0.04 | 0.41 ± 0.04 | 0.001 |
| Ferritin µg/l | 240.83 ± 213.14 | 51.56 ± 34.45 | 0.001 |
| Serum iron µmol/l | 17.55 ± 6.95 | 27.17 ± 4.84 | 0.001 |
| TIBC µmol/l | 72.35 ± 26.40 | 60.67 ± 9.02 | 0.009 |

Key: Hb = Haemoglobin, HCT = Haematocrit, TIBC = Total Iron-Binding Capacity.

Table 3. Proportions of SCA subjects with derangement in iron-related parameters

| Parameters | Below range % | Within range % | Above range % |
|-----------------------------|------------------|-------------------|------------------|
| Hb (142.5±17.5 g/l) | 100 | 0 | 0 |
| HCT (0.43±0.05 l/l) | 100 | 0 | 0 |
| Ferritin (15-250 µg/l) | 0 | 32.5 | 67.5 |
| Serum iron (11 - 27 µmol/l) | 87.5 | 12.5 | 0 |
| TIBC (45 - 72 µmol/l) | 12.5 | 40 | 47.5 |

Key: Hb = Haemoglobin, HCT = Haematocrit, TIBC = Total Iron-Binding Capacity.

Discussion and Conclusion

Sickle cell anaemia is a condition marked with haemolysis resulting in reduction of circulating red cells and the attendant oxygen supply for tissue respiration. The extent of haemolysis and the consequent severity of the ensuing anaemia varies from person to person as well as across populations. Management of sickle cell crisis spans over varied therapeutic approaches that seek to address the underlying pathophysiological factors such as pain, anaemia and arising complications. Resolving anaemia in sickle cell condition depends largely on the severity of the anaemia and often includes transfusion therapy (McGann *et al.*, 2013; Smith-Whitley and Thompson, 2012; Yazdanbakhsh *et al.*, 2012).

One of the concerns with dependence on blood transfusion is the possibility for iron overload because excess iron in the body has the potential of causing multi-organ dysfunction. However, evidence on the state of iron metabolism among sickle cell anaemia subjects varies. Although the finding of low serum iron is relatively common, serum ferritin levels appears to be unexpectedly high in most studies among sickle cell anaemia subjects (Ikusemoro *et al.*, 2014; Olaniyi *et al.*, 2014; Akinbami *et al.*, 2013; Akodu *et al.*, 2013; Koduri, 2003; Olivieri, 2001). While it may seem that previous studies have differing findings regarding iron balance in sickle cell anaemia, there are factors that may have contributed to these discrepancies. Serum ferritin, although an indicator of stored iron, is an acute phase marker of inflammation (Pretorius and Kell, 2014; Wang *et al.*, 2010; Orino and Watanabe, 2008). Its elevation may therefore not be entirely a consequence of iron overload, but may be pointing to the presence of inflammation especially as may be occasioned by the presence of infection. Observational studies may suffer from the limitation of not being able to rule out underlying factors such as presence of infection in this instance. Other factors capable of influencing the outcome of investigations on iron metabolism among sickle cell subjects include administration of transfusion therapy and whether the subjects studied were in steady state or in crisis.

There is a need to go beyond the comparison of iron parameters between sickle cell anaemia subjects and persons with normal adult haemoglobin. It has become more important to look into the proportional derangement of iron parameters within the sickle cell anaemia subjects with defined characteristics. This could represent a more sensitive approach to determining iron status in specified populations. The studied population comprised of steady state sickle cell anaemia subjects who had not received blood transfusion within the preceding one year. Majority of them had regular routine access to conventional healthcare at the University of Calabar Teaching Hospital in Calabar, Nigeria. For reasons relating to financial constraint, 17.5% of the enrolled persons could not access regular routine check at the health facility but rather visited the hospital only when they felt unwell. This distribution may not have reflected the actual access to routine checks among sickle cell anaemia patients at the hospital. It merely shows a pattern which suggests that more than 80% of those who had not been transfused in the preceding one year were accessing routine health check regularly. Thus, regular routine check could be beneficial in reducing dependence on blood transfusion therapy among sickle cell anaemia subjects.

The finding of anaemia among all the enrolled sickle cell anaemia subjects is not surprising. In fact, high packed cell volume apparently is unsuitable owing to the dangers of increased blood viscosity (Onukak *et al.*, 2019; Omoti, 2005). The goal in the management of sickle cell anaemia is therefore not to achieve high red cell values but rather to keep from sliding into severe anaemia. Majority of the SCA subjects had elevated ferritin but low serum iron levels. In normal iron metabolism, the fourfold raise in serum ferritin would have been considered indicative of high iron stores. This unfortunately appears not be translating to higher circulating iron (serum iron) among the studied population. Although the finding of low serum iron is not uncommon among SCA subjects and has been attributed to loss through haemolysis, such an observation would have co-existed with low iron stores. A possible reason for low circulating iron in the face of high iron stores could be presence

of a chronic infection among other reasons. Unfortunately, the study did not consider ruling out infections at the planning stage of the research.

This study concludes that among steady state sickle cell anaemia subjects who had not received blood transfusion within the preceding one year, more than 80% of them had regular routine access to conventional healthcare. Anaemia was present among all the enrolled sickle cell anaemia subjects, while majority of the persons had elevated ferritin but low serum iron levels.

Conflict of interest

All Authors declare no conflict of interest

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