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Impact of Medical Approach in a Limited-resources Centre on the Pattern of Sickle Cell Disease Phenotypes and its Complication in a Nigerian Hospital: A Single-center Retrospective Study

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Authors' contributions

This work was carried out in collaboration among all authors. Authors AND, AJM, TN, AOU, HCO and SO designed the study, performed the statistical analysis, wrote the protocol, wrote the first draft of the manuscript and managed the literature searches. Authors AND, CN, IOA, RO, EM, KC, NA, CRD and OO participated to the study design, data collection and analysis and authors AND, AJM and SO managed the analyses of the study and manuscript critical review. All authors read and approved the final manuscript.

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ABSTRACT

Background: Sickle cell disease (SCD) is the commonest inherited qualitative blood disorder worldwide.
Aims: To guide haematologists and other clinicians in making appropriate clinical judgement in the

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management of SCD patients in resource poor countries.
Objective: To evaluate the demographic characteristics, clinical phenotype, laboratory parameters and complications of the enrolled patients during the period of the study.
Study Design: A retrospective study.
Place and Duration of the Study: Haematology and Immunology department, UNTH over 8 years period.
Methodology: We enrolled 135 patients grouped into mild or severe SCD. The objective parameters were extracted from their case notes. Data analyzed using GraphPad Prism version 8.
Results: Of the135 subjects, 39 (29%) had mild disease while 96 (71%) had severe disease. The mean ages in the groups were 27 and 26 years respectively (age ranged from 10 to 55years). Mean weight and frequency of crises per year between the groups were 59 and 58kg, 1.0 and 5.0 crises, respectively. Significant difference existed in the mean blood counts, F = 323.3. $P < 0.0001$. Renal and liver functions showed no significant derangement. Vaso-occlusive crisis (VOC) was predominant crisis. Leg ulcer (20%) was commonest complication. Significant relationship existed between frequency of crisis and number of complications, r = 0.17, $P = .04$, [CI = 0.003 – 0.332]. No relationship was observed between the number of blood units and frequency of crisis, r = 0.05, $P = .61$, [CI = -0.12 - 0.21]. Our patients were counselled at every clinic visit with proper guidance. Significant difference existed between blood pressure and proteinuria, $P < .0001$, [CI = 4.73 – 23.2].
Conclusion: Multidisciplinary approach improved their clinical outcome. Component blood transfusion practice is strongly advocated. We recommend further studies on the psycho-socio-economic, and environmental factors that impact on clinical phenotypes of this medical condition.

Keywords: Sickle cell disease; phenotype; complications; Vaso-occlusive crisis.

1. INTRODUCTION

Sickle cell disease (SCD) is the commonest inherited qualitative blood disorder worldwide. It results from the substitution of valine for glutamic acid at position 6 of the β-globin chain [1-2]. This disorder makes the red cells to change shape under hypoxic conditions, leading to several clinical complications like vaso-occlusion, painful episodes, anaemia, stroke, and organ failure [3]. In Nigeria, about 100, 000 children are born with this disorder annually. Worldwide, about 300,000 sickle cell disease children are born [4]. The gene has a widespread distribution affecting people of Arabian, European, Oriental, and Indian ancestry [5] with males being affected more than females [6,7]. The disease has a heterogenous clinical presentation. While some patients have mild symptoms, others have severe early or late manifestations. High levels of foetal haemoglobin ameliorate the severity of the disease. [8,9].

A proposed solution that is strongly advocated include premarital counselling and testing, prenatal testing, regular medical check-ups, adherence to drug treatment and life-style modifications to ensure an optimal clinical outcome.

The severity of SCD is determined by environmental, socio-economic, geographical variables and genetic factors. Acute events in the disease include acute painful crisis, acute splenic sequestration, renal papillary necrosis, and acute chest syndrome among others [10]. These acute events over time can progress to complications like nephropathy, pulmonary hypertension, cholelithiasis, avascular necrosis of bone, leg ulcer, priapism, and stroke. There are usually periods of remission (steady state) that may be interrupted by episodes of intermittent worsening of symptoms (crisis state) [11]. Crisis is a sudden worsening of the symptoms and signs of the disease, associated with reduction in haemoglobin (Hb) level and or pain. A few precipitating factors for crisis include cold weather, dehydration, infection, physical, psychological stress, and hypoxic state [12,13]. Occlusion of blood vessel is initiated by the adhesion of young deformable red cells to the vascular endothelium followed by the trapping of irreversible sickled erythrocytes. This adhesion occurs at the post-capillary venules, and it is mediated by inflammatory cytokines and adhesion molecules, released by activated platelets, endothelial cells, and leucocytes [13,14]. This vaso-occlusive process is responsible for most of disease-related complications. Vaso-occlusive/painful crisis is the commonest type of crisis and is responsible for most hospital visits [15].

Vaso-occlusion involving the cerebral vessels may result in stroke. In SCD, stroke (ischaemic or haemorrhagic), which can occur at any age is a dreadful devastating complication frequently leading to death [12,15,16]. Ischaemic stroke is more commonly seen in young individuals unlike haemorrhagic variety which is more frequently seen in the elderly [9,12,17].

Acute chest syndrome (ACS) is a major cause of mortality [18]. It often occurs during vaso-occlusive events or in the presence of other acute illnesses [19].

The presenting signs and symptoms of ACS can vary, and individuals affected may initially have normal physical findings [20]. Several factors like fat emboli arising from infarcts in the bone marrow, infection, pulmonary embolus, and pulmonary infarction, can lead to ACS [21].

The hallmark of renal complications in SCD result from the combined effects of suboptimal renal concentrating ability and impaired diluting capacity [22,23].

The musculo-skeletal complications of the disease arise from chronic tissue hypoxia-induced changes in the bone, skin, and bone marrow. The vessel occlusion reduces the blood supply to areas distal to the obstruction causing cellular death of the affected tissue [24-26]. The main causes of bone and joint destruction in SCD include infarction of bone and bone marrow, secondary growth defects and secondary osteomyelitis [27].

Chronic leg ulcer is a common complication of SCD. It occurs in areas of the body with thin skin, and end arteries with reduced blood flow such as the malleolus [28]. It is one of the red cell-endothelial interaction dysfunctions observed in patients living with SCD [29-33].

Our objectives therefore were to evaluate the demographic characteristics, clinical phenotype, laboratory parameters and complications of the enrolled patients during the period of the study.

2. MATERIALS AND METHODS

This was a retrospective study carried out at the University of Nigeria Teaching Hospital, Ituku-Ozalla Enugu, South-East Nigeria. The study enrolled patient's records over a period of eight years, between August 2012 and July 2020. Full blood count was carried out using Mythic 22 automated blood cell analyzer, (Orphee, Geneva, Switzerland). The patients were grouped into two categories namely those with mild disease defined as having frequency of VOC between 0 – 1 per year without complication and those with severe disease defined as frequency of VOC of 2 and above per year with complication.

2.1 Statistics

We used student t-test, ANOVA F, the X^2 test to compare frequencies of occurrences, and Pearson's correlation coefficient to analyze correlation. Statistical significance was set at $P = .05$, and results were presented in tables and figures.

3. RESULTS

One hundred and thirty-five (135) SCD patients comprising 79 males (58.5%) and 56 females (41.5%) grouped into two categories of mild and severe sickle cell disease were evaluated. Out of the135 patients, 39 (29%) had mild disease comprising 25 (64%) males and 14 (36%) females with male to female ratio of 1.8:1, while severe disease was observed in 96 (71%) patients consisting of 54 (56%) males and 42 (44%) females with males to female ratio of 1.3:1. There was significant difference between patients with mild disease when compared with those that had severe disease, t = 5.816. $P < 0.0001$, [CI = 2.989 – 6.071], as shown in Table 1.

The mean age of patients with mild disease was 27 years while those that had severe disease was 26 years (age ranged from 10 to 55years). There was no significant difference between the mean ages of patients with mild disease when compared with those that had severe disease, t = 0.4017. $P = 0.6885$, [CI = -3.384 – 2.242].

There was significant difference in the frequency of crises between patients with mild disease when compared with those who had severe disease, t = 5.426. $P < 0.0001$, [CI = 2.681 – 5.758], as shown in Table 1. CI means Confidence Interval.

3.1 Haematological Parameters

Blood routine results namely haemoglobin levels (mean 7.7, range 6-9.4 g/dL), packed cell volume (mean 23.53, range 18.6 – 28.4%), total white cell (mean 6.5, range 6.5 – 17.1 x 10^9/L), with their absolute differentials: Neutrophil (mean 5.6,

range 5.0 – 6.2 x 10^9/L), Lymphocyte (mean 3.9, range 3.6 – 4.2 x 10^9/L), Monocyte (mean 0.4, range 0.3 – 0.4 x 10^9/L), Eosinophil (mean 0.2, range 0.1 – 0.3 x 10^9/L), Basophil (mean 0.10, range 0.1-0.3 x 10^9/L) and total platelet counts (mean 352, range 210 – 494 x 10^9/L), when compared between mild disease patients and those who had severe disease showed statistically significant difference among the means, F = 323.3. *P* < 0.0001. Red cell indices and mean platelet volume (MPV) were not available in the patients records.

Table 1. Comparison of Sex, Age, weight, and frequency of Crises per year across mild and severe disease groups

	Severity of Sickle Cell Disease			
Gender	Mild (%)	Severe (%)	t-test	*P* value CI
Male	25 (64.0)	54 (56.0)	5.816	<0.0001 2.981 – 6.071
Female	14 (36.0)	42 (44.0)		
Total	39 (100.0)	96 (100.0)		
Age(years)	Difference between Means 27.10	Difference between Means 26.53	0.4017	0.6885 -3.384 – 2.242
Weight(kg)	58.92	58.20	0.3953	0.6932 -4.354 – 2.903
Frequency of Crises per year	Difference between Means 1.051	Difference between Means 5.271	5.426	<0.0001 2.681 – 5.758

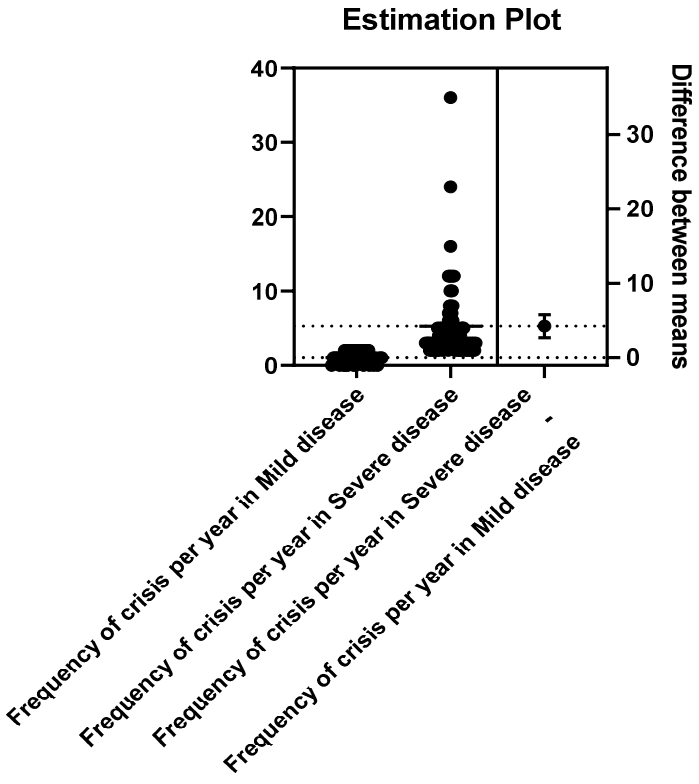

Fig. 1. is a forest plot showing comparison between frequency of crises per year across the two categories of disease severity

There was no significant difference in the frequency of blood transfusion received between the mild sickle cell disease patients when compared with their counterparts with severe sickle cell disease, t = 1.655, *P* = 0.1003, [CI = -0.2464 – 2.769].

3.2 Biochemical Parameters

There was no proteinuria in 109 (81%) subjects whereas it was present in 26 (19%) patients.

Amongst the patients with severe disease, hypertension without proteinuria was seen in 27(20%), while hypertension combined with proteinuria occurred in 22 (16%) respectively.

A statistically significant association existed between blood pressure and proteinuria, using Fisher's exact test *P < 0.0001*, [CI = 4.73 – 23.2].

A significant relationship also existed between the frequency of crisis and number of complications, using Pearson correlation r = 0.17, *P = 0.04* [CI = 0.003 – 0.332].

The analysis of variance of the frequency distribution of complications associated with the sickle cell group with severe disease showed significant difference among the means, F = 21.25. *P* < 0.0001.

Table 2. Comparison of mean values of renal and liver functions results across patients with mild and severe sickle cell disease

	Severity of Sickle Cell Disease			
Renal Function(mmol/L)	**Mild**	**Severe**	**t-test**	**P value Confidence Interval**
Sodium	140.7	138.5	2.434	<0.0163 -3.974 – 0.410
Potassium	4.444	4.309	1.576	0.1166 -3.045 – 0.034
Bicarbonate	24.28	22.29	1.376	0.1711 -4.852 – 0.870
Chloride	102.0	103.4	0.953	0.3422 -1.467 – 4.196
Urea	5.123	4.392	0.897	0.3713 -2.344 – 0.881
Creatinine	79.46	88.31	1.549	0.1239 -2.454 – 2.016
Liver Function (µmol/L)				
Unconjugated Bilirubin	14.25	14.74	0.146	0.8837 -6.133 – 7.115
Conjugated Bilirubin	16.53	14.74	0.536	0.5929 -8.370 – 4.801
Alkaline phosphatase	55.90	62.24	0.851	0.3962 -8.404 – 2.110
Alanine transaminase	13.49	11.38	0.965	0.3365 -6.443 – 2.219
Aspartate transaminase	22.03	18.16	1.284	0.2015 -9.881 – 2.092

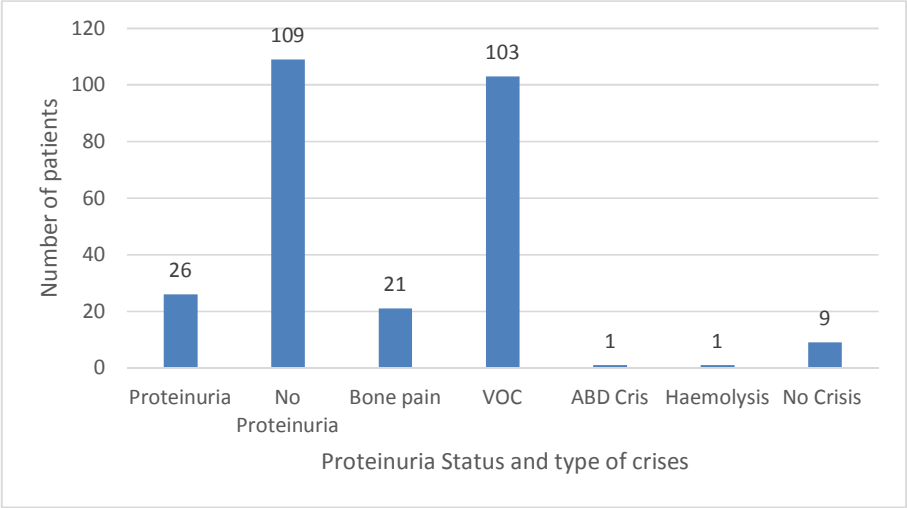

Fig. 2. Is a bar chart showing Proteinuria status and types of Sickle cell crises observed amongst the study participants

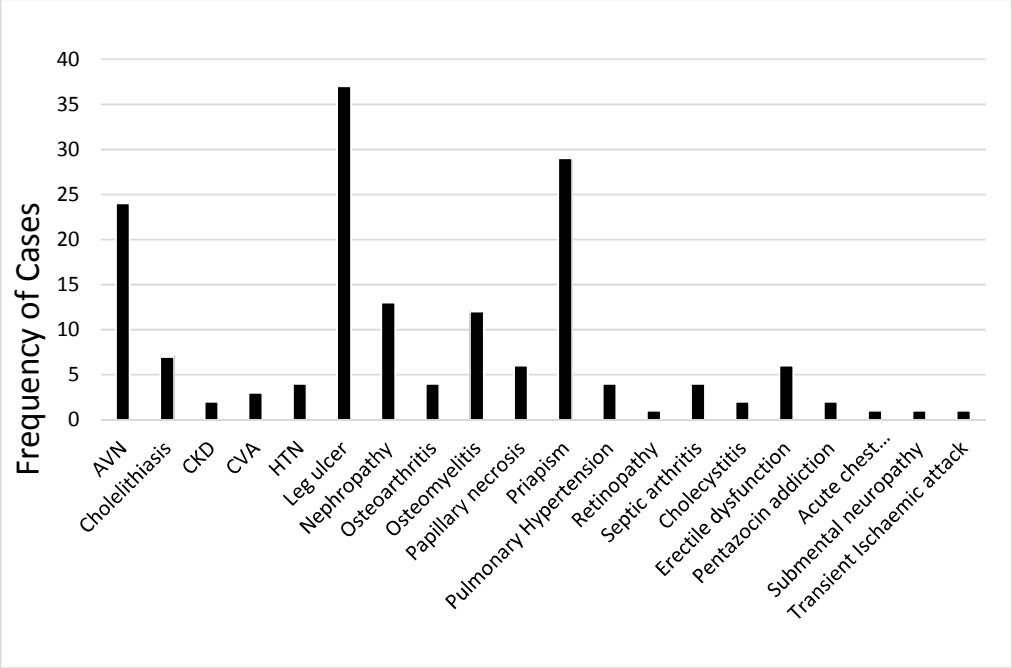

Fig. 3. Bar chart illustrating the frequency distribution of complications observed in the severe sickle cell disease group

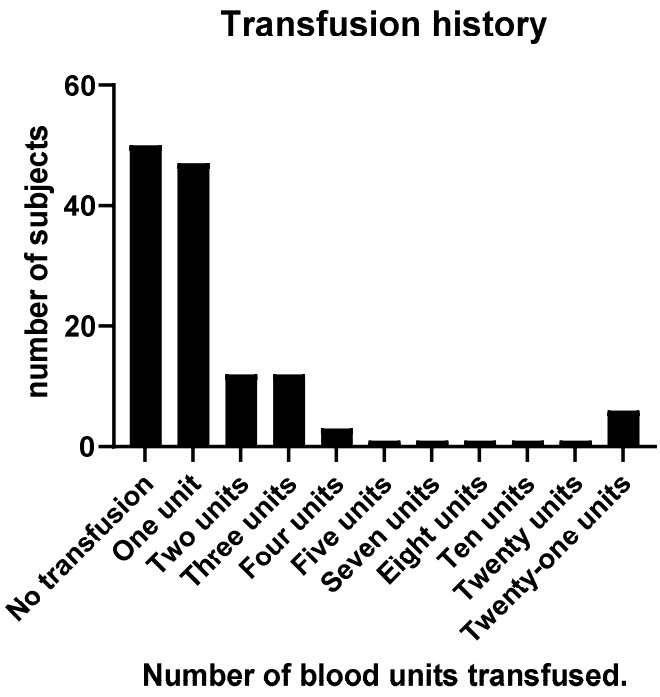

Fig. 4. Is a bar chart showing the transfusion history of the study participants

The blood transfusion services available in our center include manual exchange blood transfusion, use of whole blood, packed red cell and sedimented red cell. Occasionally, we used red cell concentrate, platelet-rich plasma, and fresh frozen plasma when our cold centrifuge was functional. Component blood transfusion services are still not the current practice in our center hence we do not use leucoreduced components.

No relationship was observed between the number of blood units received by the patients and the frequency of crisis, r = 0.05. *P = 0.61* [CI = -0.12 - 0.21].

4. DISCUSSION

Results obtained from this study showed that of the 135 subjects with sickle cell disease, 39 (29%) had mild disease comprising 25 (64%) males and 14 (36%) females with male to female ratio of 1.8:1, while severe disease was observed in 96 (71%) patients consisting of 54 (56%) males and 42 (44%) females with males to female ratio of 1.3:1 as shown in Table 1.

The disease has a heterogenous clinical presentation in which some patients have mild symptoms, others have severe early or late manifestations as was observed in this study. It may have sex predilection as more males were affected than females as shown in Table 1. These findings were corroborated with those reported by Okpala *et al.* [34], Olatunji *et al.* [6] and Akinola *et al.* [7]. The treatment of sickle cell anaemia has been a challenge despite having known the genetic basis of the disease. Based on this, their treatment has been individualized, and it varied from use of folic acid, prophylactic antimalarial drug with paludrine (proguanil), analgesics and opiods especially in those with recalcitrant bone pains. Also, we do packed red cell transfusion with occasional manual exchange blood transfusion in those with severe sickle cell anaemia. Those with leg ulcers were co-managed with plastic surgeons after review of wound swab microscopy, culture, and sensitivity results. these treatment modalities improved the quality of life in a good number of our patients who were regular to clinic follow-ups.

Our patients that had musculoskeletal complications like avascular necrosis head of femur were co-managed with the Orthopaedic Surgeons.

With each clinic attendance, our patients are usually counselled adequately on the need to be regular with their clinic appointments, adherent to their routine drugs, sleeping under mosquito-nets to prevent malaria, avoidance of exposure to cold or extreme temperatures, liberal fluid intake at least 3 liters of water per day to prevent dehydration, adequate care of their feet to avoid injuries, regular ingestion of anti-malarial prophylaxis, folic acid, early referral to obstetricians in case of pregnancy in SCD, Orthopaedics for musculoskeletal complications and plastic surgeons for leg ulcer management as well as consult to nephrologists in renal impairment, Cardiologist in hypertension and other cardiovascular events, Neurologists in cerebrovascular accidents and transient ischaemic attacks. Physiotherapist and nursing care are also integrated in our multidisciplinary management approach. This practice has improved the life expectancy of our patients with a good number living up to 55 years and above as seen in this study as shown in Table 1.

This finding agreed with the reports of Wheatherall *et al.* [4], Inusa *et al.* [5], Schnog *et al* [11], and Leikin *et al*,[15]. Improved nutrition, medical attention and awareness of this disease have also impacted on the patient's weight as was reported in this work, refer to Table 1. This finding was consistent with the work done by Adewoyin, [28].

The low haemoglobin level noted in this study, maybe because many of our patients had severe disease that maybe characterized by chronic recurrent intravascular and extravascular haemolysis. It may also be due to on-going haemolytic crisis. The raised platelet is an evidence of inflammation that characterizes SCD. The raised white cell counts as well as raised absolute neutrophil and lymphocyte counts as shown under haematological parameters in this study may be attributed to impaired immunity and recurrent infections especially malaria because we live in a resource-poor malaria endemic region.

Despite the high number of patients with severe disease and sickle cell-associated complications, there were no marked derangements in their liver and renal functions as shown in Table 2. These findings did not support numerous works done in other climes by Driss *et al,* [3], Beutler [8], Okpala [12], Ashutosh *et al* [14] and Da Silva *et al* [30]. Possible explanations for this deviation may be due to pre-analytical, analytical, or post-analytical errors.

Crises are of various types. We have vaso-occlusive crisis which results from complex interactions between the sickled cells, leucocytes, and endothelium with consequent obstruction of blood vessels. It is usually a diagnosis of exclusion especially for pains in the bones, chest, and abdomen. In this study, vaso-occlusive crisis was observed as the most prevalent crisis as shown in Fig. 2. These findings are supported by works done by Okpala et al [34], Inusa *et al.* [5], Beutler [8], and Leikin *et al*,[15]. Sequestration Crisis is another type that occurs in infants, young children and in adults with enlarged spleen due to pooling of blood in the spleen and liver. Another type of crisis is the one associated with shortened red cell life span referred to as haemolytic crisis. Here, the abnormal shape of the red cell is the reason why it is rapidly mopped up and destroyed by macrophages of the reticuloendothelial system in the spleen and liver (Fig. 2). Another type of crisis is the one known as Aplastic Crisis in which there is Parvovirus B19 infection with associated necrosis of the bone marrow.

Sickle cell patients are usually placed on daily folic acid to prevent another type of crisis known as megaloblastic crisis. In this type of crisis, marrow failure usually results from deficiency of folic acid.

Leg ulcer was the most prevalent complication observed in this study as shown in Fig. 3. It is one of the red cell-endothelial interaction dysfunctions observed in patients living with SCD and occurs in areas of the body with thin skin, and end arteries with reduced blood flow such as the malleolus. Management of leg ulcer is also multidisciplinary involving the haematologists, plastic surgeons, medical microbiologist, and wound care nurses. Second complication to leg ulcer was priapism as shown in Fig. 3. It is a manifestation of vaso-occlusive crisis in which there is occlusion of the corpora cavernosa. Third to leg ulcer is avascular necrosis followed by nephropathy. These findings were consistent with works done by Ejindu *et al* [25], Trent *et al* [29], Da Silva *et al* [30], and Chung *et al* [31].

The blood transfusion services we have included manual exchange blood transfusion, use of whole blood, packed red cell and sedimented red cell. Component blood transfusion services are still not the current practice in our center. Blood transfusion has remained a life-saving treatment modality amongst patients living with sickle cell disease Inusa *et al* [5], and Oteng-Ntim *et al* [13]. However, the absence of significant relationship between the number of blood units received by our patients and the frequency of crisis did not support previous studies. This may be attributed to alloimmunization, component of the blood unit transfused and sample size that was used in this study as shown in Fig. 4.

There was strong association between hypertension and proteinuria in this study as shown in Fig. 2, because hypertension in the presence of sickle cell disease increases the risk of damage to the kidneys. The kidney's micro-environment is a highly metabolic site that is prone to hypoxic injury which is a cardinal feature of sickle cell disease vaso-occlusion. This finding was consistent with the works done by De Jong *et al* [22] and Sheinman [23].

The significant relationship that was observed between frequency of crisis and number of complications is because most of the patients had severe disease and consequently have higher tendency for frequent crisis and complications. This finding was in keeping with various works done by Okpala *et al* [34-35], Olatunji *et al* [6] and Akinyola *et al* [7].

5. CONCLUSION

This study has been able to highlight the varied clinical phenotypes, abnormal laboratory parameters and organ damages observed in individuals with mild and severe sickle cell disease.

The improved multidisciplinary approach involving haematologists, plastic and orthopeadic surgeons, nephrologists, cardiologists, neurologists, physiotherapist, and wound care nurses in the care of the disease has improved the clinical outcome of several of our individuals living with the disease. Males were affected more than females, vaso-occlusive crisis was the most frequent type of crisis with leg ulcer being the commonest complication. Priapism with erectile dysfunction is gradually increasing in incidence.

The limitations noted in this study include incomplete data in patients case notes, financial constraints, ignorance, and low sample size.

We strongly recommend further studies on the psychological, nutritional, socio-economic, environmental, religious, geographical variables and genetic factors that impact on the clinical

phenotypes of this medical condition. Component blood transfusion practice is strongly advocated in our center.

DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

ETHICAL APPROVAL

This work was a retrospective study in which we made use of the patients' case notes only to extract the necessary data hence we sought and obtained ethical approval from the University of Nigeria Teaching Hospital Health Research Ethics Committee. The protocol number was UNTH/CSA/329/VOL.5.

CONSENT

As Per International Standard or University Standard, Patient's Written Consent has Been Collected and Preserved by the Author(S).

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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