Journal of
Blood Disorders & Transfusion

Okocha et al., J Blood Disord Transfus 2015, 6:6
DOI: 10.4172/2155-9864.1000324

Research Article Open Access

Disease Severity Scores and Haemogram Parameters in Nigerian Sickle Cell Disease Patients

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Received date: Oct 19, 2015, **Accepted date:** Dec 09, 2015, **Publication date:** Dec 14, 2015

Abstract

Background: Sickle cell disease (SCD) is associated with high mortality in Nigeria and the rest of sub-Saharan Africa; there is need to find easily available parameters that could predict disease severity and influence therapy.

Objective: To evaluate the haemogram of a population of SCD patients and correlate these with objective scores of disease severity.

Methods: Sixty (60) asymptomatic steady state (ASS) SCD patients in our clinic were randomly selected and interviewed with a questionnaire. Their haemogram was done using a 17 parameter, 3-part white cell differential, auto-analyser (KX 21N, Sysmex corporation, Chuo ku, Kobe, Japan) and objective severity scores calculated using a modification of the method proposed by Anyeagbu et al. Statistical analysis of data was done using Statistical Package for Social Sciences software, version 20 (SPSS Inc., IL, Chicago, USA), with significance assigned to p values less than 0.05.

Result: Of the 60 subjects assessed, severity scores were calculated for 49: 11 (22.4%), 31 (63.3%) and 7 (14.3%) met the criteria for mild, moderate and severe disease respectively. The haemogram parameters that were significantly positively correlated with disease severity were mean corpuscular haemoglobin concentration (MCHC), and white blood cell count (WBC), p=0.014, and 0.001 respectively. Haemoglobin concentration (Hb) and packed cell volume (PCV) were negatively correlated with disease severity (p=0.001).

Conclusion: In addition to already known haemogram parameters that affect SCD severity (such as WBC, Hb concentration, and PCV) MCHC also does same and can be manipulated by drugs and other kinds of therapy to ameliorate severity in patients.

Keywords: Sickle cell disease; Disease severity; Blood counts; Mean corpuscular haemoglobin concentration

Introduction

SCD is a disorder that presents with a wide variation of clinical features and is mostly found in developing countries where medical resources are scarce and the people mostly poor [1,2]. As a result of a number of factors, ranging from infrastructural deficits to a dearth of adequately trained manpower, the mortrality from SCD remains high in Nigeria and sub-Saharan Africa [3,4]. A number of factors including disease severity have been reported to influence the pattern of disease presentation, prognosis and survival; patients with severe disease tend to present with more complications and end-organ dysfunction [5,6]. The impact of end organ dysfunction in patients with sickle cell disease is particularly huge and is known to adversely influence disease manifestations and survival [7-9].

Recent studies has focused on evaluating ways of predicting and appropriately stratifying patients based on disease severity, with a view to identifying those that could benefit from more intense monitoring and treatment [10-12]. The observation that SCD patients (particularly children) with raised cerebral blood flow (through transcranial doppler ultrasonography) have increased risk of cerebrovascular disease has necessitated appropriate preventive treatment modifications for these group of patients with very encouraging results [10,11].

Similarly, patients indentified as having severe SCD are currently offered hydroxycarbamide (and even stem cell transplantation) with significant impact on disease prognosis [12]. In an earlier study by Okocha et al. C-reactive protein (CRP) was identified as a surrogate marker of disease severity in Nigerian patients with SCD, hence its monitoring could guide appropriate patient stratification and therapy [13]. Interesting as this observation could be however, laboratory evaluation for CRP is presently not universally available in most health care facilities in resource poor settings such as Nigeria and this may

also be the case in health institutions in the rest of sub-Saharan Africa. This therefore added more impetus to the search for a more universally available, cost effective surrogate marker of disease severity in this group of patients.

The aim of this study was therefore to correlate haemogram parameters with objectives scores of disease severity in Nigerian patients with SCD, with a view to finding cheap and universally available indices which could assist physicians in predicting severity/outcome, thereby engendering appropriate treatment modification for patients, especially in resource poor settings.

Subjects and Methods

Patient selection

Sixty (60) asymptomatic steady state (ASS) sickle cell disease (SCD) patients; 37 males and 23 females were randomly selected from our paediatric, adult and out-station clinics. ASS in our patients was defined as those who had not in the last two weeks suffered any form of crisis, had a febrile illness and not transfused in the last 3 months.

The patients or their care givers were interviewed with a questionnaire which noted at what age the patient was diagnosed, past medical history including complications such as stroke, leg ulcers, avascular necrosis of the femoral or other bones and any other condition complicating the disease. Age, sex and other demographic data were also noted. Most of the subjects were on routine drugs such as folic acid, low dose soluble Aspirin, prophylactic antimalarial drugs and omega 3 fatty acids. Ethical approval was obtained from the hospital ethical committee.

Disease severity

An objective score was calculated for disease severity by using a modification of the method proposed by Hedo et al. [14]. Scores were assigned to the following parameters: patient white blood cell count, heamoglobin levels, and number of complications suffered from. Scores of ≤3 were deemed mild disease. Scores of 3 ≥ 5 were considered moderate disease, while scores >5 were taken for severe disease.

Sample collection and laboratory analysis

Five (5) mls of blood was collected into Ethylene Diamine Tetra Acetic acid (EDTA) containers for full blood count (FBC) analysis. Analysis was done using a 17 parameter, 3-part WBC Deferential, Automated Hematology analyser (KX-21N, Sysmex Corporation, Chuo-ku, Kobe, Japan). Parameters done included packed cell volume (PCV), haemoglobin concentration, white blood cell count (WBC) and differentials, platelet count and red cell indices- mean corpuscular volume (MCH), mean corpuscular haemoglobin (MCH), and mean corpuscular haemoglobin concentration (MCHC).

Statistical analysis

Analysis of data was done using Statistical Package for Social Sciences software package version 20 (SPSS Inc., IL, Chicago, USA). Percentages, means and standard errors of mean were used to express the data obtained which were tabulated by sex, age, and other parameters that were analysed. P values were generated by comparing frequencies using Chi Square. Correlation between variables was determined using Spearman's or Pearson's correlation tests. Significance was assigned to p values less than 0.05.

Results

The mean and median ages for the subjects were 20.9 ± 10.23 and 20 years (range of 4-47 years) respectively. There was no significant statistical difference in the ages of male and female study subjects (p=0.3, Table 1).

Table 2 shows the mean and median haemogram values for the subjects. Of the 60 subjects assessed, severity scores were calculated for 49 of them; 11 (22.4%) 31 (63.3%) and 7 (14.3%) met the criteria for mild, moderate and severe disease respectively. Table 3 shows the correlation between haemogram values and disease severity. The haemogram parameters that were significantly positively correlated with disease severity were MCHC, MCV and WBC (p values=0.014, 0.025 and 0.001 respectively). Haemoglobin concentration (Hb) and PCV were negatively correlated with disease severity (p=0.001).

Table 4 shows a comparison of various haemogram parameters across different categories of disease severity, Hb, WBC and PCV remained significant (p=0.001, respectively); while MCHC was close to significance (p=0.096). Figures 1-3 are graphical representations of the relationship between disease severity score and WBC, Hb and PCV respectively in study subjects.

Parameters	N	Mean	Standard Deviation	Median	P-value
Age	60	20.86	10.23	20	
Female	23	22.68	8.09	18	0.297
Male	37	19.78	11.28	11.5	

Table 1: Age and Sex distribution of Subjects.

Parameters	N	Mean	Standard Deviation	Median
PCV	60	0.23	0.05	0.23
HB	60	7.37	1.74	7.2
WBC	60	12.72	5.18	11.6
RBC	60	2.79	0.73	2.74
Platelet	60	327.08	133.37	338
MCV	60	86.48	9.13	86.35
MCHC	60	31.71	2.29	31.7
MCH	60	27.44	3.23	26.7

Table 2: Mean and Median values of Haematological Parameters of subjects.

Parameters	Pearson's correlation	P-Value
Severity score vs MCH	-0.025	0.885
Severity score vs MCV	0.289	0.025
Severity score vs MCHC	0.315	0.014
Severity score vs RBC	0.141	0.284
Severity score vs Platelet	0.154	0.241
Severity score vs PCV	-0.554	*0.001
Severity score vs HB	-0.714	*0.001
Severity score vs WBC	0.631	*0.001
*significant p-values.		

Table 3: Correlation of severity score with some haematological parameters.

Parameters	Mild disease	Moderate disease	Severe disease	P-value
RBC	1.63 ± 0.314	1.62 ± 0.27	2.01 ± 0.40	0.82
Platelet	243.97 ± 191.90	253.94 ± 187.48	222.71 ± 152.55	0.926
PCV	0.26 ± 0.05	0.20 ± 0.04	0.19 ± 0.04	*<0.001
HB	8.9 ± 1.49	6.60 ± 1.02	6.04 ± 1.35	*<0.001
WBC	7.11 ± 5.63	14.15 ± 3.48	17.54 ± 7.35	*<0.001
MCV	86.43 ± 8.86	87.78 ± 7.78	83.49 ± 13.42	0.632
MCH	28.24 ± 3.28	26.94 ± 2.94	26.57 ± 3.88	0.422
MCHC	32.55 ± 2.16	30.77 ± 2.29	32.00 ± 2.29	0.096
*significant p-values.				

Table 4: Comparison of different haematological parameters by disease severities.

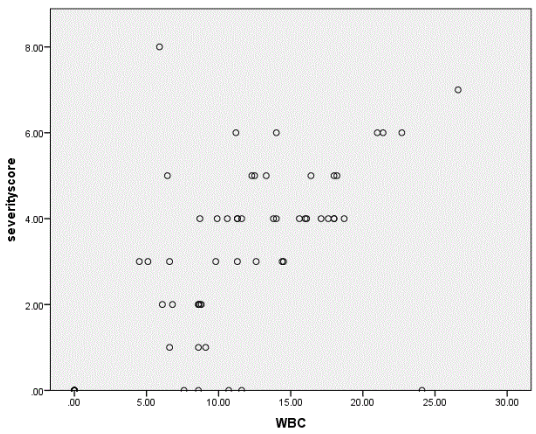

Figure 1: Association between white blood cell count (WBC) and severity score.

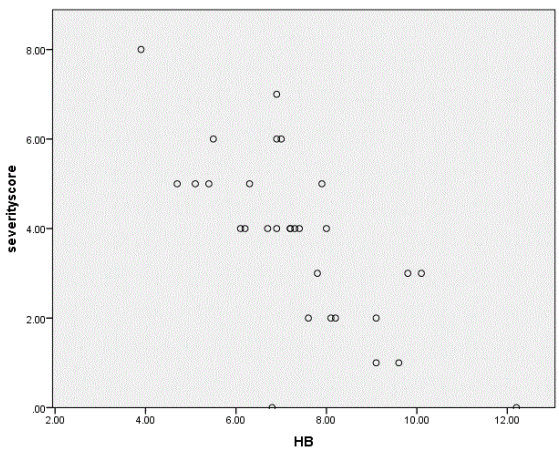

Figure 2: Association between Haemoglobin (HB) levels and severity score.

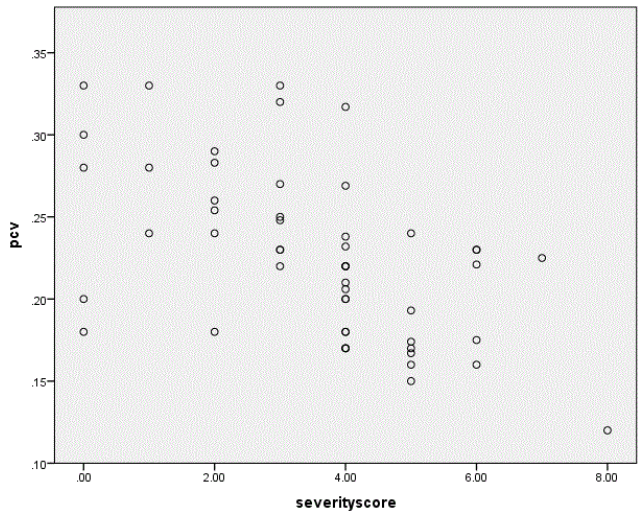

Figure 3: Association between PCV and severity score.

Discussion

SCD is a disease entity that is caused by a point mutation at the sixth position of the β haemoglobin chain; causing glutamine to be replaced by valine in this position. This disorder is quite heterogeneous, with marked variations in both disease manifestation and clinical severity. Though many theories have been advanced to explain these variations, none has satisfactorily done so. In this work, an objective severity score was calculated and correlated with haemogram indices. Interestingly, after applying statistical methods, we observed that PCV, Hb, WBC and MCHC significantly correlated with disease severity (Tables 3 and 4). These findings are exciting because these parameters are available in most laboratories especially in developing countries (including Nigeria and the rest of sub-Saharan Africa) which have the highest burden of SCD.

MCHC is the amount of haemoglobin present per unit volume of packed red cells. It has been observed that low MCHC tends to be associated with an increase in deformability of red blood cells while higher values correlated with increased rigidity (less deformability). [15] More so, an increasing body of evidence has shown that overt iron deficiency in SCD appears to ameliorate disease severity [16,17]. In the light of the above, a number of workers have thus hypothesized that this observed clinical benefit may result from a decrease in MCHC with increased red cell deformability and whole blood rheology [18,19]. This phenomenon can be explained firstly, by understanding that when Hb S is deoxygenated, there is some delay before polymerization begins. This is called the delay time and it has been shown to be directly proportional to $10^{\times 30}$ of the intracellular Hb concentration [20], therefore small decreases of MCHC can appreciable increase delay time; such that it may become less than capillary transit time. This will prevent polymerization, sickling, membrane damage and subsequently reduce haemolysis and therefore ameliorate severity. Intravascular red cell sickling with subsequent cell membrane damage (leading to sickle vasculopathy) and haemolysis are established pathways to sickle cell related end organ damage and thus have significant influence on disease severity and patient survival [21,22].

In addition, evidence exists to show that in SCD, erythrocytic Hb-S concentration reduces the oxygen affinity of the blood thereby increasing the release of oxygen to end tissues [23]. Correspondingly, it has also been found that as MCHC increases, blood O_2 affinity decreases with increased tendency for red cell sickling [24]. May et al. argued that this phenomenon may be due to the fact that high MCHC levels encourage polymerization of sickle haemoglobin (which is an initiating step in red cell sickling) [25]. Hydroxyurea is well known for its effect in ameliorating the clinical presentation of SCD and one of the mechanisms by which this comes about is by reducing the MCHC [26]. Therefore, the identification of the MCHC as a surrogate marker of disease severity in this study is not surprising, in view of its established influences on red cell deformability, haemoglobin S polymerization and tendency to sickling.

Packed cell volume, Hb concentration and WBC are well known parameters that affect severity in SCD [27-29]. Hence we used Hb concentration and WBC as parameters in our calculation of an objective severity score.

Limitation of the study

This work is limited by the fact that some of the data we collected were based on recall of our patients or their care givers, more so, a larger study size population could have given the work more power to detect significant results.

Conclusion

In addition to well known haemogram parameters such as WBC, Hb concentration, and PCV, this work clearly shows that MCHC equally affects severity in SCD. The MCHC is measured by most automated heamatology analysers and it could equally be calculated manually, using the Hb concentration and PCV. This makes it available to physicians and other health professionals who care for patients with SCD, even in resource poor settings. Importantly, the MCHC is amenable to manipulation by drugs and other kinds of therapies and this could potentially be explored with a view to ameliorating disease severity in patients with SCD.

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