Evaluation of Clinical Severity of Sickle Cell Anemia in Sudanese Patients

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Abstract

Sickle cell anemia (SCA) is an inherited disease characterized by a complex and varied physiopathology and exhibits wide clinical diversity. SCA's variability poses significant management challenges to caregivers and physicians alike. Different scoring systems have been used for the assessment of the severity of the disease since evaluation of disease severity in patients with SCA will help to identify patients at higher risk for an adverse clinical course who may need more active management and monitoring.

In this study we tried to introduce a modified scoring system to evaluate the clinical severity of SCA in Sudanese patients using simple clinico-pathological parameters linking clinical severity to some hematological parameters. The total severity score of the 131 patients studied ranged from 1 to 19, with mean ± standard deviation of (11.7 ± 4.91) and median of 12.0. One hundred and three patients (78.6 %) had either moderate disease 87 (66.4%) or severe disease 16 (12.2%), while 28 (21.4%) had mild disease according to this severity score grading system. Among the severe group the frequency of males was 3 times that of females. Dactylitisas the first manifestation of disease revealed the highest frequency and almost all of the affected patients (44/49) had moderate and severe disease. Total white blood cell count and absolute neutrophil count were significantly higher while hemoglobin concentration was significantly lower among those with severe disease.

Key Words: Severity score, Sickle cell anemia, Sudan

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Introduction

Sickle cell disease is a collective name for a group of conditions causing clinical symptoms that are characterized by the formation of sickle red cells (Lewis, 2006). The highest prevalence of Hb S is in tropical Africa and among blacks in countries that participated in the slave trade. It occurs with lower frequency in the Mediterranean basin, Saudi Arabia, and parts of India(Greer, 2003, Ciesla, 2007).

The heterogeneous phenotype in patients with sickle cell disease (SCD) is determined by the interaction of genetic and environmental factors, of which some have been identified (Platt et al., 1994, Miller et al., 2000, Steinberg and Rodgers, 2001, Sebastiani et al., 2005, Sebastiani et al., 2007). SCD varies in clinical severity from the virtually symptomless to the potentially lethal state characteristic of sickle cell anemia. Some die in the first few years of life, while others have been discovered late in life as a result of a chance survey (Makani et al., 2007). It is essential to know which determinants are associated with severe disease, so that prognostic models can be constructed and appropriate management given, such as a chronic transfusion program, hydroxyurea treatment, or bone marrow transplantation. These prognostic models may help to identify patients who are at increased risk for a severe disease course before irreversible organ damage has occurred. Such patients may benefit from early treatment with disease modifying therapies (Tweel, 2009) . SCA severity assessment may also provide the data needed for comparing SCA patient's characteristics as well as clinical courses in different geographical locations. Sophisticated genetic, molecular, and biochemical analyses, such as determining the number of deleted α-thalassemia genes, the β-globin gene haplotype, and fetal cell production (FCP) loci, are frequently utilized in studies designed to identify risk factors that predict the severity of SCA among children in developed countries (Tweel, 2009, Jastaniah, 2011) . A valid index in this field should distinguish patients according to their severity status, cumulative up to the time point when outcome is evaluated, covering all items

that are apparently important, and demonstrate a high correlation with similar measurements of severity. The severity measured by such an index can then be used as an outcome measure in etiological research when determinants of "a severe phenotype" are studied (Tweel, 2009).A number of severity scores have been proposed, aiming at the integration of many clinical and laboratory dimensions into a meaningful single synthetic measure of morbidity and/or risk of death within a given period (Coelho et al., 2012) .In Saudi Arabia clinical and hematological presentation of sickle cell disease (SCD) was assessed. The individuals identified as Hb S homozygotes were investigated further. The patients were further classified on the basis of whether there was associated alpha- or beta-thalassemia. A severity index (SI) was calculated for each patient and the clinical presentations and laboratory findings were compared. White blood cells (WBC) level correlated positively with the SI. The lowest SI values were encountered in patients with associated alpha-thalassemia who also had the lowest WBC count and mean cell volume (MCV) and the highest red blood cell (RBC) count and packed cell volume (el-Hazmi, 1992a) .The clinical profile of sickle cell disease in Yemeni children was evaluated by measuring the percentage of patients with different clinical manifestations in different ages, presenting symptoms, number of hospital admissions, distribution of SCD complications and the degree of consanguinity (Al-Saqladi et al., 2009) . Xandra W. et al developed an index consisting of 12 items the index clearly differentiated patients by genotype ($P < 0.01$) or a-gene deletions ($P < 0.01$). The correlation with hospitalization was moderate. Age and the risk of death score were weakly associated with the pediatric severity index for SCD (van den Tweel et al., 2010). Also Adegoke SA et al, introduced a scoring system to evaluate the clinical severity of SCA in Nigerian children using simple clinico-laboratory parameters, and related the severity to their sociodemographic, hematological**,** and biochemical profiles where the total severity score of the 115 children ranged from 0 to 34 (Adegoke and Kuti, 2013). In this study we tried to evaluate the severity of SCA in Sudanese patients using a modified scoring system based on simple clinico-pathological parameters, relating clinical SCA severity to some hematological parameters.

Materials and Methods

This study was conducted at Jaafer Ibn Aouf Pediatric Hospital over a period of eight months (May to December 2014). All SCA patients (hemoglobin genotype SS) attending the study

area during this period who accepted to participate in the study were included. Verbal consents were obtained from the accompanying parent of each participant. A pretested and validated structured questionnaire was used to obtain age, gender, tribe, residence, current clinical profile, and past medical history, including information on the age at first diagnosis. Severity of SCA was assessed using both clinical and laboratory parameters. The 3 major areas assessed included:

a. The current hematocrit, and total white blood cell count.
b. Frequency of blood transfusion, and hospitalization in the previous 12 months and through life.
c. Lifetime cumulative incidence of complications.

For each child, lifetime cumulative incidence of specific complications of SCA, as described by the SCD cooperative study group (Ballas SK. et al., 2010), such as cerebrovascular disease (CVD), acute chest syndrome (ACS), gall stones, osteomyelitis, chronic leg ulcer, and priapism, were documented. Events were confirmed by review of past medical histories and by checking the medical records of all patients.

Scoring of the parameters

A total of 8 parameters were assessed to reflect each patient's present state, and lifetime complications. Items were scored according to the frequency of occurrence and severity, with scores ranging from 0 to 5, as shown in (Table1). Acute life-threatening events and neurological complications were assigned higher scores; for instance, CVD was assigned a score of 5. The total score was then calculated for each patient (range from 0 to 24), and the disease was categorized as mild when the total score was < 8, moderate when the total score was 8 to17 and severe when the total score was > 17.

Laboratory investigation

Standard laboratory methods were used to determine hemoglobin concentration, hematocrit concentration, red cell count, total white blood cells count, platelets count, red cell indices, absolute neutrophils and lymphocytes counts at the time of presentation. Data analysis was performed using SPSS for Windows software version 20. Means, standard deviations (SD), and percentages were determined. Means ± SD were compared using independent t-test. The relationship between disease severity score and continuous variables such as age was assessed using Pearson correlation analysis values of P less than 0.05 were considered statistically significant.

Table 1: SCA Scoring System

1. For number of previous transfusions per life score:
- 0 when number is 0
- 1 when number is 1/whole life
- 2 when number is 2/whole life
- 3 when number is 3/whole life
- 4 when number is 4/whole life
- 5 when number is more than 5/whole life

2. For number of previous transfusions in last year score:
- 0 when number is 0
- 1 when number is 1/year
- 2 when number is 2/year
- 3 when number is 3/year
- 5 when number is > 3/year

3. For number of previous hospitalizations, score:
- 0 when number is 0
- 1 when number is 1/whole life
- 2 when number is 2/whole life
- 3 when number is 3/whole life
- 4 when number is 4/whole life
- 5 when number is more than 4/whole life

4. For packed cell volume, score:
- 0 when ≥ 24%
- 1 when 18–23%
- 2 when < 18%

5. For white blood cell count, score:
- 0 when < 11,000/mm3
- 1 when between 11,000 and 15,000/mm3
- 2 when > 15,000/mm3

6. For lifetime cumulative incidence of specific complications, score:
- 5 when CVD is/was present, 0 when absent
- 3 each when gall stone, chronic leg ulcer, osteomyelitis, priapism is/was present, 0 when absent.
- 1 when steady state is present, 0 when absent.

Results

One hundred and thirty-one patients comprising 64males and 67 females were recruited. The mean age (± SD) of the patients was 8.3 ±4.4 years (rang: 2 months - 26 year). There was significant difference in the mean age between males and females:(7.34± 3.91) years for boys and (9.37± 4.67) years for females (t = 0.008) with the male being younger. (Table 2) School-age patients were more frequently represented, being (n= 66; 50.4%) of patients, followed by preschool-age (n = 34;25.9%) and adolescents (n = 31; 23.7%). (Table 3)

SCA severity score

The total severity score ranged from 1 to 19, with a mean ± SD of (11.7 ± 4.91) and median of 12.0. One hundred and three patients (78.6 %) had either moderate disease 87 (66.4%)or severe disease 16 (12.2%), while 28 (21.4%) had mild disease. (Table 3) Forty (30.5%) of the131 patients had CVD (ischemic type).

Socio-demographic variables and disease severity score

Gender, age and geographical origins did not statistically influence disease severity score (Table 3). Although the ranges of the severity score among the males (4-19) and females (1-19) were close, the difference between them was nearly significant (P= 0.07). Among the sever group the frequency of the male was 3 times the female (male 12, female 4). (Table 3)

Almost half of the moderate and most of the severe groups were within the school age patients (moderate: 43/87, sever: 11/16), but no statistically significance difference between the different age groups considering the severity scores (P=0.534). (Table 3)

The original home for most of the study population was western Sudan 98/131. Of them (n=78;82.1 %) had moderate and severe score. (Table 3)

Age and signs at first presentation and disease severity score

The patients whose ages were less than one year at the first presentation had the highest moderate and severe scores: 80/87 (61.1%), 14/16 (10.7%) respectively. Of the patients whose ages were more than one year at first presentation 11/20 had mild severity score. Statistically significant difference was found between the two groups of ages considering the severity scores (P =0.0001). Forty-nine patients (37.4 0%) had dactylitis / hand-foot syndrome as the first manifestation of disease revealing the highest frequency among the other findings. Of them 44 patients (33.6%) had moderate and severe disease. There was no correlation between age at first presentation and disease severity score (Correlation= -0.107). No statistically significant difference between clinical findings at first presentation and severity score (P=0.319). Table (4)

Hematological parameters and disease severity score

Total white blood cell count, absolute neutrophil count, and hemoglobin (Hb) concentration revealed statistical significant difference among the severity score groups. P values =0.0001, 0.003 and 0.006 respectively. The severe group had the highest means of WBCs and absolute neutrophils and the lowest mean of Hb concentration Table (5).

Table (2): Age and gender distribution among the study population

	Sex	N	Mean	Std. Deviation	P-value
Age/year	Male	64	7.34	3.913	
	Female	67	9.37	4.677	**0.008**

P-value is considered significant if it is less than 0.05 (sig<0.05)

Table (3): Socio-demographic variables and disease severity score

	Total score			Range of score	P-value
	Mild	**Moderate**	**Severe**		
Gender					
Male	14(10.7%)	38(29.0%)	12(9.2%)	4- 19	**0.070**
Female	14(10.7%)	49(37.4%)	4(3.1%)	1-19	
Total	28(21.4%)	87(66.4%)	16(12.2%)	1-19	
Age					
Preschool	8(6.1%)	24(18.3%)	2(1.5%)	2- 19	0.534
School age	12(9.2%)	43(32.8%)	11(8.4%)	2- 19	
Adolescence	8(6.1%)	20(15.3%)	3(2.3%)	1-18	
Total	28(21.4%)	87(66.4%)	16(12.2%)	1-19	
Original home	**Mild**	**Moderate**	**Severe**	**Total**	
North	0	1 (100)	0	1(100%)	
South	1 (20%)	4 (80%)	0	5(100%)	
West	17(17.9%)	66(69.5%)	12(12.6%)	95(100%)	
East	2(50%)	0	2(50%)	4(100%)	0.134
Center	8(30.8%)	16(61.5%)	2(7.7%)	26(100%)	

P-value is considered significant if it is less than 0.05 (sig<0.05)

Table (4): Age and signs at first presentation and disease severity score

	Total score					
	Mild	**Moderate**	**Severe**	**Range of score**	**P-value**	**Correlation**
Age at first presentation					**0.0001**	
≤ 1 year	17(13.0%)	80(61.1%)	14(10.7%)	1-19		
>1 year	11(8.4%)	7(5.3%)	2(1.5%)	1-18		
Total	28(21.4%)	87(66.4%)	16(12.2%)	1-19		
Clinical findings at first presentation						
Fever	9(6.9%)	24(18.3%)	5(3.8%)	1-19	0.319	-0.107
Dactylitis	5(3.8%)	38(29.0%)	6(4.6%)	2-19		
Pain	8(6.1%)	17(13.0%)	3(2.3%)	2-18		
Anemia	3(2.3%)	4(3.1%)	0	1-17		
Others	3(2.3%)	4(3.1%)	2(1.5%)	4-18		
Total	28(21.4%)	87(66.4%)	16(12.2%)	1-19		

P-value is considered significant if it is less than 0.05 (sig<0.05)
Strong correlation (1- 0.5), Moderate correlation (0.5- 0.03), Weak correlation (0.3- 0.1)

Table (5): Hematological parameters and disease severity score

	Mild Mean±SD	**Moderate Mean±SD**	**Severe Mean±SD**	**P-value**
WBCs	12.77± 4.22	14.32± 4.48	18.35± 2.68	**0.0001**
RBCs	2.92± 0.69	2.91± 2.40	2.37± 0.41	0.593
HGB	7.74± 1.61	7.21± 1.08	6.41± 1.02	**0.003**
HCT	24.04± 4.55	25.01± 23.32	19.53± 3.43	0.581
MCV	84.55± 7.88	86.31± 7.48	85.57± 6.88	0.556
MCH	27.21± 3.09	28.14± 7.21	27.48± 2.35	0.758
MCHC	31.86± 1.30	32.13± 2.59	32.06± 1.75	0.888
PLT	446.75± 141.88	420.15± 154.0	472.88± 266.61	0.456
LYMN	6.18± 3.74	6.62± 3.26	7.34± 2.74	0.537
MXDN	1.53± 0.73	1.68± 1.11	2.07± 0.84	0.360
NEUTN	5.35± 2.47	5.86± 2.39	11.81± 11.55	**0.006**

P-value is considered significant if it is less than 0.05 (sig<0.05)

Discussion

This study showed the variability in the severity pattern of SCA in Sudanese patients using a scoring system based on simple clinico-pathological parameters. Most of the patients were from the western Sudanese tribes (98/131) which have the highest incidences of hemoglobin S due to consanguineous and intertribal marriages. Of them (n=78;82.1 %) had moderate and sever score. (Table 3)

One hundred and three patients (78.6 %) had either moderate disease 87 (66.4%) or severe disease 16 (12.2%), while 28 (21.4%) had mild disease. (Table 3) Forty (30.5%) of the131 patients had CVD (ischemic type). To our knowledge this is the first study in Sudan to evaluate the severity of SCA in children using a comprehensive scoring system based on simple clinico-pathological parameters. Different severity index/scoring systems have been reported to classify SCA severity among Saudi Arabian, Yemen, Nigerian and Senegalese children (el-Hazmi, 1992a, Al-Saqladi et al., 2009, el-Hazmi, 1992b, Diop et al., 1999, Adegoke and Kuti, 2013) . It is noticeable that we don't have infants in our study population and only (23.7%) adolescents. These figures are much less than those from the USA and other developed countries. This may be related to the significant reduction in infant deaths in the USA due to effective cord blood screening programs, early detection, vaccination against pneumococcus, and use of prophylactic antibiotics (Al-Saqladi et al., 2007) . These screening and early comprehensive programs are not readily available in our locality. Thus, children in our area are screened only when there is suspicion of hemoglobinopathies.

Our patients tended to have more severe disease (average disease severity score of 11.7 ± 4.91) than the Senegalese, Yemeni, eastern Saudi Arabian, southwestern Province in Saudi Arabia and Nigerian children whose average scores were 7.8, 5.8, 4.5, 9.5 and 9.5 respectively (el-Hazmi, 1992a, Al-Saqladi et al., 2009, Adegoke and Kuti, 2013). This variability has been linked to several genetic factors, such as differences in β-globin haplotype polymorphisms in patients residing in different geographical locations (el-Hazmi, 1992a). Other genetic abnormalities, such as glucose-6-phosphate dehydrogenase deficiency, thalassemias, or other abnormal hemoglobin variants, also may alter the clinical presentation of SCA (Adegoke and Kuti, 2013) .

Gender did not statistically influence disease severity score (Table 3). The difference between males and females was not significant (P = 0.07). Among the severe group the frequency of males was 3 times that of females (male 12, female 4). (Table 3) This is different from some earlier reported findings that showed that pre-adolescent girls had more severe disease.

(Ballas, 2001) Although there was no statistically significant difference between the age groups (preschool, school, and adolescence) considering the severity scores (P=0.534), almost half of the moderate and most of the severe groups were within the school age patients (moderate: 43/87, severe: 11/16), (Table 3. These results almost go with the Nigerian findings that revealed positive correlation between age and severity score. (Adegoke and Kuti, 2013)

The patients whose ages were less than one year at the first presentation had the highest moderate and severe scores: 80/87 (61.1%), 14/16 (10.7%) respectively. These findings reveal that the earlier the symptoms appear the higher the severity score is. Of the patients whose ages were more than one year at first presentation 11/20 had mild severity score. Statistically significant difference was thus found between the two groups of ages considering the severity scores (P =0.0001). These results are in contrast with the Nigerian findings who reported that age at diagnosis did not affect disease severity. (Adegoke and Kuti, 2013)

Forty-nine patients (37.4 0%) had dactylitis / hand-foot syndrome as the first manifestation of disease revealing the highest frequency among the other findings. Of them 44 patients (33.6%) had moderate or severe disease, Table (4).This goes with the findings of other workers who found dactylitis positively correlated with disease severity(Ballas, 2001). Earlier reports have shown that infants who develop dactylitis in the first year of life are approximately 3-times more likely to have an adverse outcome and tend to have a severe course of illness which may include a cerebrovascular accident when older .(Ballas, 2001)

Also, Dactylitis/hand-foot syndrome as the first manifestation, was present in 33% of the Nigerian patients, and it was positively correlated with disease severity. Dactylitis/hand-foot syndrome is an early manifestation of vascular obstruction in the bone marrow of small distal bones in infants and young children (Al-Saqladi et al., 2007) . It is usually present as an initial condition in geographical locations where more severe disease is prevalent (south-western Saudi Arabia, Jamaica, West Africa) (Jastaniah, 2011, Al-Saqladi et al., 2007), but is rarely seen where disease is generally considered to be mild, such as eastern Saudi Arabia(Al-Saqladi et al., 2007, Adegoke and Kuti, 2013). Total white blood cell count, absolute neutrophil count, and hemoglobin (Hb) concentration revealed statistical significant difference among the severity score groups. P values = 0.0001, 0.003 and 0.006 respectively. Leukocytosis, neutrophilia, and anemia were more frequent in patients with severe and moderate disease in this study (Table 5). These findings are in agreement with the Nigerian results (Adegoke and Kuti, 2013). These hematological abnormalities, especially polymorph nuclear leukocytosis, have been associated with an increased risk of early death and the development of lifetime complications such as stroke, priapism, and ACS (Miller et al.,

2000). Increased adhesion of polymorph nuclear leucocytes and platelets to the vascular endothelium is implicated in the initiation and propagation of painful crises (Miller et al., 2000).

This simple disease assessment scoring system would be very easy to adopt in settings where other more sophisticated tests are not feasible. However, more valuable scoring can be performed by including other laboratory parameters such as bilirubin level and Hb F level, molecular and genetic factors.

Competing interests

The authors declare that they have no competing interests.

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