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# Clinical Manifestations of Children with Sickle Cell Disease in the Northern and Western Regions of Yemen

**Ahmed Hamood Alshehari[1*], Hana Ali Mohammed Sabbar[2]**

[1] Pediatric Department, Faculty of Medicine, Thamar University, Dhamar, Yemen
[2] Pediatric Department, Al-Jomhouri University Hospital, Sana'a, Yemen

**For Correspondence:**
Ahmed Hamood Alshehari *
Pediatric Department, Faculty of Medicine, Thamar University, Dhamar, Yemen
Tel: +967 777 902 255
Email: Shehari250@yahoo.com

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## Abstract

**Background:** Sickle cell disease (SCD) is characterized by a wide variation in the clinical manifestations and severity of the associated complications despite the molecular abnormality leading to sickle gene is similar in all haplotypes.
**Aim:** This study aimed to evaluate the clinical manifestations patterns of children affected by homozygous SS SCD.
**Methods:** It was a hospital-based, cross-sectional study carried out on 147 pediatric patients from the time of birth up to 12 years. It was conducted at Saudi Hospital Hajjah (SHH) over a period of a year (2020).
**Results:** The mean age was 7.32 ± 3.5 years, 57.1% of them were males. Two children (1.3%) had their symptoms started at the first year of age. The most frequent symptoms were vaso-occlusive crises (VOC), generalized bone pain (38.0%), fever (34.0%), bone pain and fevers (9.5%), anemic crises (7.5%) and hand-foot-syndrome (6.1%). Splenomegaly was detected in 28.5% and cerebrovascular accident (CVA) in one child (0.7%). Splenomegaly as well as bone pain were significantly observed among children older than five years ($P < 0.05$).
**Conclusion:** SCD is characterized by a marked variations in the clinical manifestations. The symptoms started as early as the first year of life and VOC remain the most frequent clinical presentation. Genetic counseling, premarital screening as well as early infant screening are urgently required in our country to reduce the magnitude of disease and to improve the quality of care.

**Keywords**: Sickle Cell Disease, Yemen, Vaso-Occlusive Crises

## 1. Introduction

Introduction Sickle cell disease (SCD) consists of a group of hemoglobinopathies in which individuals inherit hemoglobin variants derived from single point mutations, that causes morphological abnormalities in the red blood cells (RBC) [1]. Sickle cell anemia (SCA) is characterized by the homozygosity for hemoglobin S (HbS) and is the most frequent and severe form of the disease. A single base-pair point mutation (GAG to GTG) results in the substitution of the amino acid glutamic acid to valine in the 6th position of the β-chain of hemoglobin referred to as hemoglobin S (HbS) [2]. This results in deoxygenation- induced polymerization and finally result in the abnormal crescent shape of RBCs that can occlude small blood capillaries causing vaso-occlusive crisis (VOC), ischemia, and tissue damage; also, this sickled hemoglobin makes RBCs vulnerable to broken easily result in extravascular and intravascular hemolysis with a result of low hemoglobin level [2,3]. SCD nearly affects all body organs with many complications such as VOC, acute chest syndrome (ACS), gallstones, stroke, and others [4].

The disease mainly affects tropical regions, particularly sub-Saharan Africa, India and the Middle East, but it is also found in the Mediterranean area. The distribution of the disease in these regions is thought to be due to the so-called "Malaria hypothesis" which stated that there is a partial resistance of HbS carriers to all forms of *Plasmodium falciparum* malaria so that individuals

heterozygous for HbS might have had a selective advantage during malaria epidemies, thus perpetuating the mutated allele [5].

The incidence of SCD in the Arabian Peninsula ranged from 1.2 to 2.6%. In Saudi Arabia, the prevalence of SCD varies significantly in different parts of the country, with the highest incidence reported in the Eastern province [6]. Clinical manifestations are markedly heterogeneous and the disease pattern and severity vary widely between individuals in different socio-economic and geographical locations. The major symptoms of SCD are mild to severe anemia, painful crises, frequent infections, hand and foot syndrome and stroke [7]. In the published study of White and coworkers [8] the frequency of SCD in Yemen was reported as 0.95 per cent. Disease course and severity were similar to that in Africans and American blacks and western parts of Saudi Arabia [9]. In the individuals with SCD, the prevalence of Xmn I polymorphic sites was be similar to the prevalence reported in the south-western region of Saudi Arabia [10] and α-gene deletion occurred at a higher prevalence in Yemeni patients with SCD [11]. The aim of this study was to evaluate the clinical presentation of children having SCD and to find out the gender – related difference of such symptoms in our center.

## 2. Methods

This is a cross-sectional study conducted at Saudi Hospital Hajjah (SHH) over a period of a year (2020). SHH provides health care services free of charge and serves people of the Northern and Western governorates of the country (Hajjah, Al Hudeidah, Sa'dah, Amran, and Al-Mahweet). The protocol of this study was approved by the hospital ethics committee. We retrospectively collected data of the children who diagnosed as having SCD from their database of the hospital. The sample of this study included all children with symptomatic SCD (HbSS), aged between 6 months to 12 years. The diagnosis of SCD followed in our hospital was depend on positive sickling test and confirmed by hemoglobin electrophoresis. The data retrieved included age, gender, family history, clinical presentation, complications, investigation, number of previous admission and outcomes. The clinical presentation was categorized as VOC crises, infection, anemic crisis and complications such as cerebrovascular accident (CVA) among others. The children aged was categorized for the purpose of comparison as ≤ 5 years and > 5 years old. The investigation extracted were all hematological and biochemical tests available in the patient's database. All patient's information were collected in a standard data sheet. We excluded from this study all cases with inadequate information available in their files. The clinical severity of the subjects was assessed based on the frequency of episode, hospitalization, blood transfusion and complications.

Data were analyzed using the Statistical Package for the Social Sciences (SPSS) version 20.0 software (IBM, Armonk, New York, USA). Chi-square test, t-test and Fisher exact tests were used as appropriate. The data are presented as mean ± standard deviation or frequencies and percentages. A *P* value of 0.05 or less was considered statistically significant.

## 3. Results

The A total of 147 Children with HbSS were studied, 84 males and 63 females. The mean age was 7.32 ± 3.5 years (range 1-12). Of these, 36.0% were ≤ 5 years old. All children evaluated were Yemeni. More than a third of children (38.7%) had positive consanguinity history and the second-degree relative accounted for the majority (28.6%), (Table 1).

**Table 1: Baseline characteristics of children with sickle cell disease**

| Parameter | Frequency (%) | *P* value |
|---|---|---|
| **Sex** | | |
| Male | 84 (57.1) | 0.080 |
| Female | 63 (42.9) | |
| **Age (year)** | | |
| ≤ 5 | 53 (63.0) | < 0.001 |
| 6 – 12 | 94 (63.9) | |
| Mean ± SD | 7.32 ± 3.5 | |
| **Family history** | | |
| None | 90 (61.2) | < 0.001 |
| 1st degree | 4 (2.7) | |
| 2nd degree | 42 (28.6) | |
| 3rd degree | 11 (7.5) | |

Two children (1.3%) had developed the initial symptoms during their first year of age whereas 31.2% had become symptomatic during the first 5 years and all patients developed the clinical manifestations by the age of 8 years. The commonest clinical manifestation observed was VOC crises as bone pain (38.0%) followed by fever for investigation (34.0%). Bone pain associated with fever was the clinical manifestation among 9.5%. Abdominal pain and Hand-foot syndrome were presented in equal proportions (6.1 %). Anemic crises was shown among 7.5% of patients. The hemoglobin level of these patients was ≤ 6 g/ dl. Seven children (4.7%) had malaria and one child (0.7%) admitted with overt CVA. Spleen was palpable among 38.5% of children. There was no significant age-related difference of the symptoms except for bone pain and splenomegaly which observed more frequently among children > 5 year (*P* < 0.05) (Table 2).

**Table 2: Clinical presentation according to age category**

| Clinical presentation | Total | ≤5 year | > 5 years | *P* value |
|---|---|---|---|---|
| **Vaso-occlusive crises** | | | | |
| Bone pain | 56(38.0) | 21(14.2) | 35(23.8) | 0.03 |
| Bone paint + Fever | 14(9.5) | 5(3.4) | 9(6.1) | 0.27 |
| Abdominal pain | 9(6.1) | 2(1.3) | 7(4.7) | 0.08 |
| Hand-foot-syndrome | 9(6.1) | 5(3.4) | 4(2.7) | 0.72 |
| **Anemic crises** | 11(7.5) | 6(4.1) | 5(3.4) | 0.75 |
| **Fever** | 50(34.0) | 21(14.2) | 29(19.7) | 0.20 |
| **Malaria** | 7(4.7) | 3(2.0) | 4(2.7) | 0.69 |
| **CVA** | 1(0.7) | 1(0.7) | 0 | 0.31 |
| **Follow –up** | 1(0.7) | 0 | 1(0.7) | 0.31 |
| **Splenomegaly** | 42(28.5) | 10(6.8) | 32(21.7) | 0.00 |

CVA: cerebrovascular accident

Table 3 shows the distribution of clinical symptoms according to gender. There was no significant gender-related difference of the symptoms (*P* > 0.05). The mean hemoglobin level was 7.72 ± 1.68 g/d. Only six children

(4.0%) had Hb > 10 g/dl. Seven children (4.7%) had severe anemia (Hb < 5 g/dl), whereas 26.5% had Hb in the range of 5-7 g/dl. Blood transfusion was required for 120 children (81.6%), the frequency of transfusion between 1-5 times was 60.5% and > 5 times was seen in 21.0%. There was a history of previous one hospitalization in 31.2 %, third admission and more was detected in (20.4%). All children improved by symptomatic measures and simple blood transfusion, Table 4.

**Table 3: Clinical presentation according to gender**

| Clinical presentation | Total | Male | Female | *P* value |
|---|---|---|---|---|
| **Vaso-occlusive crises** | | | | |
| Bone pain | 56(38.0) | 34(23.1) | 22(14.9) | 0.06 |
| Bone paint +Fever | 14(9.5) | 7(4.7) | 7(4.7) | 1.0 |
| Abdominal pain | 9(6.1) | 5(3.4) | 4(2.7) | 0.72 |
| Hand-foot-syndrome | 9(6.1) | 4(2.7) | 5(3.4) | 0.72 |
| **Anemic crises** | 11(7.5) | 6(4.1) | 5(3.4) | 0.75 |
| **Fever** | 50(34.0) | 25(17.0) | 25(17.0) | 1.0 |
| **Malaria** | 7(4.7) | 4(2.7) | 3(2.0) | 0.69 |
| **CVA** | 1(0.7) | 1(0.7) | 0 | 0.31 |
| **Follow -up** | 1(0.7) | 1(0.7) | 0 | 0.31 |
| **Splenomegaly** | 42(28.5) | 19(12.9) | 23(15.6) | 0.50 |

**Total 4: Hematological parameters, blood transfusion and frequency of admission**

| Parameter | Number | % | P value |
|---|---|---|---|
| **Hb (g/dl)** | | | |
| < 5 | 7 | 4.7 | |
| 5 – 7 | 93 | 26.5 | |
| 8 – 10 | 95 | 64.6 | <0.001 |
| > 10 | 6 | 4.0 | |
| Mean ± SD | 7.725 ± 1.68 | | |
| HbS % | 80.82±13.8 | | |
| HbF % | 11.9±4.06 | | |
| **Frequency of blood TX** | | | |
| 0 | 27 | 18.3 | |
| 1 – 5 | 89 | 60.5 | <0.001 |
| > 5 | 31 | 21.0 | |
| **Severity** | | | |
| Mild | 46(31.2) | | |
| Severe | 101(68.7) | | |
| **Frequency of admission (previous year)** | | | |
| 1st | 71 | 48.2 | 0.010 |
| 2nd | 46 | 31.2 | |
| 3rd and more | 30 | 20.4 | |

TX: Blood transfusion

# 4. Discussion

Results from the present study showed that male patients were more predominant than females with male to female ratio is 1.3:1. This is consistent to another study from India which reported male to female ratio as 1.5:1 [12]. Sickle cell disease (SCD) is inherited as autosomal recessive and affects men and women equally [13]. Therefore, the difference in the incidence between male and female might reflect the difference in the population analyzed and sample size. The present study found that the mean age of children investigated was 7.32 ± 3.5 year and the maximum incidence of SCD was seen between 6 - 12 years (63.9%). This is comparable to Telfer et al [14] who reported the mean age of children with SCD living in England as 7.8 (interquartile range 3.3 - 13.0). For decades, the morbidity and mortality of SCD were highest during the first 3 years of life but the recent advance in the management, recommendations, and guidelines have greatly delayed the onset of episodes in the early age period and led affected children to living into adulthood [15]. Such improvement could partly explain the high frequency of the affected children seen at age 6-13 years. Another explanation is that the early onset of disease might be not severe enough to warrant hospitalization.

This study found that more than a third of patients (38.7%) their parents had positive consanguinity, and the second-degree relative accounted for the majority. This result is in line with that reported from Saudi Arabia where 75.8% of the sickle cell patients have a positive history of consanguinity [16]. It is well known that consanguinity is associated with significantly higher rate of inherited blood disorders including SCD [17]. In Yemen, consanguineous marriage is prevalent which can result in multiplication of SCD incidence. We suggest therefore, that premarital screening and genetic counseling are important in situation of high-risk marriages.

Age-related symptoms seen in the current study revealed that two children (1.3%) presented with symptoms during the second half of the first year of life, 46 children (31.2%) developed their symptoms during the first five years of age and all pediatric patients had become symptomatic by age of 8 years.

The clinical presentation of patients with SCD is a spectrum of manifestations ranging from acute generalized pain to early onset of stroke, leg ulcer and multi-organ damage [18]. The commonest manifestation observed in the present study was bone pain (38.0%) followed by fever (34.0%). Pain crises was the most common symptoms accounted for almost 60% of the subjects. A study from Jazan region, Saudi Arabia [16] described similar findings, the VOC was 58.2%. Another study from Yemen [19]. reported the main causes of hospitalization were VOC (30.0%), anemic crisis (16.0%) and acute chest syndrome (11.0%). Telfer et al. [14] from UK reported that the pain crises was the most frequent presentation among pediatric from 0 to 16 years. Patients with SCD may experience severe pain early in infancy, childhood, and adulthood and is associated with negative impact in patients' quality of life [18].

Pain results from stimulation of nociceptive nerve fibers caused by micro vascular occlusion. Obstruction of the microcirculation by sickling RBCs results in low blood flow to the organs which result in ischemia, edema, pain, necrosis and organ damage [18,20]. Though bone pain was present in all ages, it is observed significantly higher among children older than 5 years (p 0.03) indicating chronicity and the progression of the pathological process. Fever was the second most common symptom in our analysis. Elobied et al [21] reported that fever was the most frequent presenting complaint (52%) which is consistent with our result. Fever > 38.5 Ċ in the background of SCD especially in younger children is considered medical emergency because it can be a first sign of bacteremia and

requires evaluation promptly [22,19]. Although infection is the major etiology, other complications should not be overlooked. There was neither age nor gender significant difference related to fever seen in our study. Bone pain associated with fever also observed less frequently. Dactylitis (hand-foot-syndrome) was seen among 6.1% of children with no significant age-related or gender related difference ($p > 0.05$). Similar finding was reported from a study performed in Yemen [19]. Hand-foot syndrome in the early year of life is a cardinal feature of vaso-occlusion of post capillary vasculature resulting in tissue edema and pain of the extremities [23]. There is evidence that the syndrome carries a significant risk for development of cerebrovascular accident (CVA) in older children with a relative risk of adverse outcome as 2.6 [19]. Anemia is one of the commonest symptoms of SCD particularly in homozygous HbS, and is the major cause of morbidity and mortality [24].

The present study detected 7.5% of the children had anemic crises. Al Saqladi et al [19] from Yemen, reported that anemic crises were the presenting symptom in 15.8% of SCD children. This rate is more than double the rate seen in our result indicating difference in SCD phenotype, and severity of cases among children investigated. Anemic crises is triggered by the rate of fall from individual steady state hemoglobin level which varies according to the phenotype, ranging from levels as low as 60–80 g/L for homozygous S to 100–110 g/L in double heterozygous SC [25]. Malaria was observed among 7 children (4.7%), 2.7% of these were aged ≤ 5 years and 2.0% aged > 5 years old with no significant difference (*P* 0.69). SCD increases susceptibility to infections by bacteria, sepsis, and malaria in children under 5 years age [26]. It has long been assumed that malarial infection is a major cause of morbidity and mortality among SCD patients. However, a study from Kenya [27] found that the incidence of malarial parasitemia was lower among children with SCD compared to children without SCD. This finding indicates a high susceptibility of patients with SCD to lower level parasitemia and severe manifestation of malaria in homozygous cases. It has been suggested that HbAS protects against malaria but the mechanism is not completely understood. It is probably including reduced parasite growth and enhanced removal of the parasitized cells through innate or acquired immunological processes [28]. However, the finding of malaria in our cases suggests the presence of HbS/βo or HbS/β+ or it might be related to frequent blood transfusion.

Splenomegaly is a common clinical manifestation in SCD because the spleen is the first organ affected by SCD complications. Before age of 12 months, the majority of children have spleen dysfunction. There is evidence that as many as 90% of SCD patients develop persistent splenomegaly [29]. The present study detected that 28.5% of children had splenomegaly. In Saudi Arabia the rate of 30 to 55% has been reported [30]. Certain acute and chronic events could be responsible for splenomegaly such as fibrocongestion, hypersplenism, malarial infection, and high level of HbF > 20% [29]. On the other hand, persistent splenomegaly may lead to frequent hemolytic episodes and acute splenic sequestration [29]. Splenomegaly was significantly higher among pediatrics of > 5 years (p 0.00) suggesting that age is a significant factor associated with splenomegaly.

Stroke is a significant complication in SCD associated with a potential of major morbidity and mortality [31]. The reported incidence of overt stroke is 11.0% by age < 20, and the silent stroke is more frequently reported in up to 30% [31,32]. Overt stroke can lead to motor disability, neuropsychological impairment and death [31]. This study found one male of 3 years old had overt stroke. The low rate of stroke complication seen in this study is more likely reflecting the underreporting secondary to poor health care utilization in our situation. Taking in account that occurrence of stroke is associated with permanent neurological injury thus, screening of the stroke using transcranial Doppler (TCD) is appropriate to avoid the significant alteration of educational attainment, and quality of life.

Chronic blood transfusions have been demonstrated to reduce the crises, stroke and prevent repeated acute chest syndrome [15]. Our study showed that 60.5% of patients had a frequency of blood transfusion between 1-5 times and 21.0% had transfused more than 5 times during the previous vaso-occlusive and anemic crisis. These findings are comparable to a study from Saudi Arabia [32,21]. Another recent study from Yemen by Saqladi et al [33] revealed that the most common indications for blood transfusion among children with SCD was anemic crisis (41.1%) followed by VOC (13.8%), and acute chest syndrome (11.3%). However, the high frequency of blood transfusion suggests severe complications and correlate inversely with Hb levels at the time of admission.

Our analysis showed that 31.2% were admitted to the hospital previously during the last year, and 20.4% had three or more hospitalizations. The most common cause of admission was acute pain crises giving an annual average of crises as 1.7 regardless of the gender. These findings are supported by other previous work which reported the average annual crises as 0.4 to 0.8 per patient [34].

This study found that the folic acid supplementation and penicillin prophylaxis were prescribed monthly to all pediatric patients. In addition, hydroxyurea is prescribed for children beyond 5 years age who experienced frequent crises.

The clinical manifestation of SCD is highly variable and influenced by the haplotype of the beta gene. Data addressing the sickle cell gene in Yemen are very few. The studies from Saudi Arabia have shown that the most predominant haplotype is the African haplotype, more likely the Benin haplotype in the western parts which is historically part of Yemen [35]. Presently, these parts have borders overlap with the areas where our study was carried out. Furthermore, the clinical manifestations observed in our study are similar to those reported in the western parts of Saudi Arabia supporting haplotype similarity. It is found in our analysis that 68.7% of pediatric patients had severe clinical course which agrees with the

evidence reported that in our regions, the severe pattern of the clinical course is predominate [36]. This illustrates the influence of environmental factors such as infections, nutrition, and socioeconomic states on the course of disease.

Given that SCD is highly prevalent in our country combined with high consanguineous marriages, certain measures seem appropriate to minimize the occurrence as well as burden of SCD on the public health.

For this purpose, premarital screening and genetic counseling are urgently needed for the high-risk marriage. In addition, infant screening program should be developed to reduce the SCD related morbidity and mortality. Public and couple awareness of the transmission potential of SCD should be enhanced through promoting the education about SCD inheritance and understanding the serious morbidity. A notional registry of SCD in Yemen that can be used to identify the cases and classify the SCD variants currently does not exist. Establishment of the registry program can also help provide patients with a better care. Our study is limited by its nature as a hospital-based therefore, the pediatric patients evaluated were representative of the population of those governorates served by the hospital. Further studies in different areas of Yemen are needed to estimate the true prevalence of SCD and to help provide a firm information on the manifestations and disease severity. Also, the intensity of pain in crises was not assessed because of the retrospectively designed study as the data regarding pain scoring did not exist.

# 5. Conclusion

SCD is a serious health problem associated with severe morbidity. There is a diverse clinical presentation, the most frequent symptom observed is vaso occlusive crises, followed by fever and anemic crises. Premarital screening program is urgently needed in our setting where a high rate of consanguineous marriage is being exist. Infant screening is important for early diagnosis and treatment.

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**Competing interests**
The authors declare that they have no competing interests.

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