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REVIEW AND CLINICAL ASSESSMENT OF PATIENTS WITH SICKLE-CELL DISEASE AT CHILDREN'S HOSPITAL

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Abstract

Objective: To determine the epidemiological pattern of hemoglobinopathies: sickle cell anemia (SCA), sickle cell trait (SCT), and hemoglobin C, at the Children's Hospital in Benghazi Libya.
To see the Geographical distribution of cases and the percentage of each type, their race, and the clinical course of the disease.

Methods: The information was initially collected retrospectively through hematology clinic records and was refined prospectively with data collected from the patients during their visits in the last 5 months. The study was focused on the symptomatic (SCA) cases only.

Results: In the clinic, a total of 78 files of hemoglobinopathies, SCA (58), SCT (13), hemoglobin C+S (5), hemoglobin C trait (2). The age of evaluation ranged from 6 months – 26 years with a mean of 10.84 ±SD 6.75. Mean of hemoglobin 7.5±2 SD. The male to female ratio was 1:1.4. For each patient, the number of admissions ranged from 1-10 times with a mean of 2.6 admissions, and the frequency of blood transfusions ranged from 0-10 times. Complications included cholelithiasis (4.8%), stroke (hemiplegia) (9.5%), hepatitis B&C (9.5), HIV (3.1%), hypersplenism (6.3%), acute chest syndrome (6.3%), (1.2%) died from overwhelming sepsis (post-surgical splenectomy syndrome) within 6 months period.

Conclusion: Almost all the cases are originally from the Sahara and the south areas, of African descent, poor school performance. Symptomatic cases only registered, not adequately managed, higher percentage of consanguinity, National register for Hemoglobinopathies to facilitate the development of a national program for the control of the disease by preventing carrier marriage.

keywords: sickle cell disease, sickle cell anemia, consanguinity, chronic pain, hemoglobinopathies, anemia

Introduction

The chronicle of sickle cell anemia first began in 1910 with a report by James Herrick in Chicago on the clinical manifestation and the sickled appearance of the red blood cells of a student with recurrent bouts of pain and anemia. Despite being reported in 1910, disease manifestation had been recognized long before in Africa, where different tribes bestowed on the malady various onomatopoetic appellations that evoked the basic nature of recurrent pain. The importance of deoxygenated blood of sickled red cells was first appreciated in 1927 when Hahn and Gillepsie demonstrated that oxygen deprivation-induced a sickle-like deformation that was enhanced both by acidic pH and was reversible on reoxygenation.

Sickle cell disease (SCD) is an inherited multisystem disorder with its cardinal features being chronic hemolytic anemia and recurrent painful episodes related to the presence of mutant sickle sequential effects of the A→T nucleotide substitution in the 6th codon of the B globin, gene substitution of valine for glutamic acid on the outer surface of the HbS molecule leading to reduced solubility and polymerization of HbS when deoxygenated sickling and poor deformity of polymer containing erythrocytes and occlusion by sickle red cell of microvasculature (1, 2, 3).

In 1956 and 1958 Ingram, identified the substitution of the 6th codon for glutamic on the B-globin chain while the polymerization sickling doctrine had come full circle. The earlier observation by Diggs and Bibb of a population of irreversibly sickled cells (ISCS) that would not revert to discocytes with reoxygenation forewarned that sickle cell pathophysiology was too complex to be explained by polymerization alone (2, 3, 4).

The first evidence that sickle cell anemia is inherited was derived from unaffected parents and relatives could be made to sickle, a phenomenon proposes "active" and latent varieties of sickle cell disease. In 1949, the conclusion that sickle cell anemia results from homozygous inheritance of a genetic determinant heterozygous parents were reached independently by Beet, Neel, Pauling, and colleagues who found that patients with sickle cell anemia have all HbS but the parents have both HbS and HbA (5, 6, 7, 8, 9). This study was conducted to assess the epidemiological pattern and the magnitude of the problem of sickle cell disease in Libya. The study was concentrated on the geographical location in terms of the residence and location of the patients to examine the distribution of sickle cell disease patients in differing regions within Libya.

Malaria Hypothesis

Allison found that the stable frequency of sickle cell gene existing in areas of hyper-endemic falciparum malaria, was the result of a balance between gene exclusion from the premature death of homozygote and gene selection from the resistance of heterozygotes against death from malaria, thereby defining the concept of genetic polymorphism. Children with sickle cell trait have lower rates of parasitemia and cerebral malaria. The mechanism by which the sickle cell gene protects against malaria is not understood although rigid sickle cell trait red cells may repel parasitic invasion.

G6PD Deficiency.

The influence of glucose-6-phosphate dehydrogenase (G6PD) deficiency, another common African polymorphism, on the epidemiology, expression, and frequency of the sickle cell gene has been a mantle of debate. G6PD deficiency was reported to have a greater frequency among sickle cell disease patients. More recent reports have emphasized that the detection of G6PD deficiency is easily confounded by the young age of circulating sickle erythrocytes and has not confirmed a higher frequency of the mutant G6PD gene.

Pathophysiology of SCD

The rigid sickle cell is easily damaged by mechanical stress during its passage through the vasculature. The result is chronic hemolytic anemia within a rate of red cell destruction at two to eight times the normal rate. The degree of anemia is relatively constant in any individual unless cell production is suppressed – for example, by infection – or less commonly, if the rate of hemolysis increased. The latter may occur during infection which increases oxidative stresses on the red cells already predisposed to oxidant injury. Because of decreased deformability, the sickle erythrocyte is susceptible to entanglement and sequestration wherever blood flow is sluggish such rigid misshapen cell, altered blood viscosity and compromised blood flow. These alterations often to the extent of producing ischemia, thrombosis, vaso-occlusion, and infarction.

Enhanced adherence of sickled red cells to vascular endothelial is thought to be an important initiating factor in vaso-occlusive events. Whether other extra erythrocyte factors, such as hypercoagulable state, thrombocytosis, and abnormalities in the microcirculation may also contribute to vascular stasis and occlusion is not known.

Conversion of red blood cells from normal biconcave disks to sickle forms requires deoxygenation of hemoglobin which leads to polymerization of soluble deoxyhemoglobin into a gel. In the gel phase, polymerized sickle hemoglobin forms parallel fiber bundles that distort the cell into a sickle shape. Polymerized sickle hemoglobin can convert to the soluble form upon reoxygenation, allowing the cell to return its original unsickled shape.

Approximately 10 % of circulating erythrocytes, however, remain irreversibly sickle despite reoxygenation. Irreversibly sickling is related to a change in the cell membranes and HbS within oxygenated.

The sickle shaped cells seen on the peripheral blood smear are an example of irreversibly sickled cell. In mixed venous blood, however, where the oxygen is about 40 mmHg, as many as 40 % of red cells may be sickled. Most of these cells reverted to a normal discoid shape upon reoxygenation in the pulmonary circulation leaving only irreversibly sickled cells to be found in the arteries. The tendency of red blood cells to sickle is strongly related to the concentration of HbS within the cells, therefore, hypertonic dehydration promotes sickling. Percentage of fetal Hb diminishes the concentration of sickle Hb and, because of interaction between sickle and fetal Hb, also decreases polymerization of sickle hemoglobin (1, 2, 3, 4, 11, 12).

Clinical Manifestations

The clinical manifestations of sickle cell disease vary tremendously between and among the major genotypes. Even within the genotype regarded as being most severe—sickle cell anemia—some entirely asymptomatic patients are detected only incidentally, whereas others are disabled by recurrent pain and chronic complications. Patients are typically anemic but lead an asymptomatic life punctuated by painful episodes. Virtually every organ system in the body is subject to vaso-occlusion, which accounts for the characteristic acute and chronic multisystem failure of this disease. Important clinical features less directly related to vaso-occlusion are growth retardation, psychosocial problems, and susceptibility to infection (12, 13).

Life Expectancy

In 1973, Diggs reported that the mean survival of patients with sickle cell disease was 14.3 years; in 1994 Platt et al. reported a life expectancy of 42 years for men and 48 years for women with sickle cell anemia. Prolonged survival over the past 20 years is more the result of improved general medical care than of successful anti-sickling therapy. The ability of prophylactic penicillin therapy to prevent mortality from pneumococcal sepsis may now be having an impact on survival (14, 15).

Anemia

Chronic hemolytic anemia is a hallmark of sickle cell disease. Sickle erythrocytes are destroyed randomly with a mean life span of 17 days. The survival of irreversibly sickled cells (ISCs) is much shorter than of other sickle cells. The overall hemolytic rate reflects the number of ISCs. Anemia is most severe in sickle cell anemia and HbS- B-thalassemia. In addition, erythropoietin levels are inappropriately low, more severely so in adults than in children, suggesting the presence of subclinical renal disease. The lower erythropoietin levels may reflect the suppression effect of increased blood viscosity on erythropoietin production. Hemolytic anemia may be exacerbated by any of several events: aplastic crises and acute splenic sequestration or, less commonly, sequestration in other organs, chronic renal disease, bone marrow necrosis, deficiency of folic acid or iron, and hyper-hemolysis (15, 16).

Aplastic and Hypoplastic Crises.

Human parvovirus B19, which specifically invades proliferating erythroid progenitors, is very important in these syndromes. Parvovirus B19 accounts for 68% of aplastic crises in children with sickle cell disease, but the high incidence of protective antibodies in adults makes parvovirus a less frequent cause of aplasia in older patients. Bone marrow necrosis, an event characterized by fever, bone pain, reticulocytopenia,

and a leucoerythroblastic response, also causes aplastic crisis. This may also be the result of parvovirus infection. The mainstay of treating aplastic crises is red cell transfusion. When transfusion is necessitated by the degree of anemia or cardiorespiratory symptoms, a single transfusion usually will suffice, since reticulocytosis resume spontaneously within a few days. Transfusion may be avoided by keeping severely anemic patients at bed rest to prevent symptoms and by avoiding supraphysiologic oxygen tensions (15, 16).

Splenic Sequestration and Hyper-hemolytic Crises.

Acute splenic sequestration is characterized by an acute exacerbation of anemia, persistent reticulocytosis, a tender enlarging spleen, and sometimes hypovolemia. Patients susceptible to this complication are those whose spleen has not undergone fibrosis—young patients with sickle cell anemia and adults with Hb SC disease or sickle cell- B-thalassemia Sequestration may occur as early as a few weeks of age and may cause death before sickle cell disease is diagnosed. In one study, 30% of children had splenic sequestration over a ten-year period, and 15% of the attacks were fatal. The basis of therapy is to restore blood volume and red cell mass. Alternatively, chronic transfusion therapy can be used in young children to delay splenectomy until it can be tolerated safely Because recurrence may occur during the course of transfusion therapy, parents should be trained to detect rapidly, enlarging spleen and to seek immediate medical attention in this event. Less common sites of acute sequestration include the liver and possibly the lung.

Hyper-hemolytic crisis is defined as the sudden exacerbation of anemia with increased reticulocytosis and bilirubin level. In one report, seven of the eight children with hyper-hemolysis had G6PD deficiency. In the presence of hyper-hemolysis, it is probable that many cases are related to some complicating etiology such as G6PD deficiency or immune hemolysis.

Chronic worsening of anemia may be due to developing renal insufficiency or deficiency of folic acid or iron. Inadequate erythropoietin renal failure results in deficient compensation for sickle cell hemolysis. Chronic hemolysis results in increased utilization of folic acid stores, and megaloblastic crises from folic acid deficiency have been reported. Despite increased intestinal absorption of iron in sickle cell disease, the combination of nutritional deficiency and urinary iron losses results in iron deficiency in 20% of children with sickle cell disease. The diagnoses of iron deficiency may be obscured by the elevated serum iron levels associated with chronic hemolysis, necessitating the detection of a low serum ferritin or elevated serum transferrin for the diagnosis (15, 16, 17).

Acute Painful Episode.

Acute pain is the first symptom of disease in more than one-fourth of patients. It is the most frequent symptom after 2 years of age, and the complication for which patients with sickle cell disease most commonly sought medical attention. Although a general correlation of vaso-occlusive severity and genotype has been posited, tremendous variability occurs within genotypes and in the same patient over time. In one large study of patients with sickle cell anemia, one-third rarely had pain, one-third were hospitalized for pain approximately two to six times per year, and one-third had more than six hospitalizations pain – related hospitalization per year. The frequency of pain peaks between the ages of 19 and 39 years. After the age of 19, more frequent pain is associated with a higher mortality rate. Over a 5-year period in the National Cooperative Study of Sickle Cell Disease, 40% of patients had no painful episodes and 5% of patients accounted for one-third of the emergency department visits, and pain frequency correlated with high total hemoglobin levels and low HbF levels.

Pain may be precipitated by events such as cold, dehydration, infection, stress, menses, and alcohol consumption, but most painful episodes have no identifiable cause. It can affect any area of the body (most commonly the back, chest, extremities, and abdomen), may vary from trivial to excruciating, and is usually endured at home without a visit to the emergency department. Painful episodes are events caused by vaso-occlusion. Frequent pain generates feelings of despair, depression, and apathy, which interfere with everyday life. This scenario may lead to chronic debilitating pain syndrome, which, fortunately, is rare. Approximately

one-half of episodes present with objective clinical signs, such as fever, swelling, tenderness, tachypnea, hypertension, nausea, and vomiting. The most promising laboratory indicators of acute vaso-occlusion are changes in the distribution of sickle cell subpopulations and rheologic properties of the blood.

Growth and Development.

By the age of 2 years, children with SCD have detectable growth retardation, which affecting weight more than height and has no gender difference. Skeletal maturation is delayed sexual maturation is retarded with elevated gonadotropin level, with delayed menarche in girls, these related to the degree of hemolysis due to increased basal metabolic requirement of the patients. There have been reports of response to folic acid and zinc supplementation (17,18).

Infections.

Infection is the major presenting manifestation of sickle cell anemia in early childhood. The most common complication requiring hospitalization and the most frequent cause of death at all ages is infection. S.pneumoniae is the most common cause of bacteremia in children with sickle cell disease. Haemophilus influenzae bacteremia affects older children. It is less fulminant than s.pneumoniae bacteremia but it can be fatal.

Meningitis in sickle cell anemia is a problem if infants and young children is caused most frequently by S. pneumoniae and occurs in the setting of bacteremia. Rapid administration of antibiotics has resulted in a lower incidence of meningitis among bacteremic patients. Osteomyelitis occurs more commonly in SCD as a result of infection of the infracted bone and commonly caused by salmonella species (19, 20).

Complications of Sickle Cell Disease

Neurological Complications

Stroke is one of the major complications of SCD, occurring in 25 % of patients. Although full recovery may follow the crisis, incomplete resolution of neurologic deficits is the more common experience. Children have higher oxygen demands than adults making a child with SCD at an increased risk of developing a stroke.

In early ischemia (less than 3 hours), CT may be negative. At this moment in time, an MRI may provide better details of the area of ischemia. Magnetic resonance angiography (MRI) show large vessel occlusion disease or aneurysm (21, 22, 23, 24, 25, 26).

Acute Chest Syndrome and Pulmonary Complications

The lung is a major organ for acute and chronic complications in sickle cell disease. Acute chest syndrome is a frequent cause of death in both children and adults, characterized by fever, respiratory symptoms, accompanied by infiltration on the lung. The highest incidence is seen in winter where respiratory infections are more frequent (27).

Hepatobiliary Complications

Chronic hemolysis is associated with a higher incidence of pigmented gall stones. Biliary sludge is a viscous material detectable by ultrasound and maybe a precursor of gall stone development. Fulminant hepatitis is unusual but, about 65% will develop chronic hepatitis and cirrhosis (27, 28).

Priapism

Defined as a sustained, painful and unwanted erection, priapism is due to vaso-occlusion which causes obstruction of the venous drainage of the penis. It develops in patients with lower HbF, reticulocytosis ,

increases platelet count and HbSS genotype. Priapism can be either acute, chronic and recurrent which may result in fibrosis and impotence (28, 29). The mean age at which priapism occurs is between the ages of 12-20.

Cardiac Complications

Systolic murmurs are found in most patients due to chronic anemia while the exercise capacity of patients is diminished. It appears that when increased oxygen demand exceeds limited oxygen-carrying capacity. There is a risk of myocardial infarction despite normal coronary arteries (32).

Diagnosis

Hemoglobin concentration usually ranges from 5 to 9 g/dL. The peripheral blood smear will typically contain large cells, poikilocytes, and irreversibly sickled cells. Reticulocyte counts usually range from 5 % to 15 %, and nucleated cells and Howell Jolly bodies are often present. The total white cell count is elevated. The platelet count is usually increased. The sedimentation rate is slow. The bone marrow is markedly hyperplastic. Roentgenograms show expanded marrow spaces and osteoporosis. The diagnosis is established by hemoglobin electrophoresis or thin layer isoelectric focusing and solubility testing. The majority of screening programs use isoelectric focusing from the dried blood spots. It is imperative that all infants including those born at home be screened before any blood transfusion. It is found that parents at risk of having a child with sickle cell disease were interested in prenatal diagnosis and would consider termination of pregnancy from the affected fetus.

The first successful prenatal diagnosis relied on obtaining a fetal blood sample for analysis of globin chain synthesis. Fetal DNA samples are obtained by chorionic villus sampling at 10 – 12 weeks' gestation. Neonatal screening should be requested for all high-risk infants such as those of African, Mediterranean, Middle Eastern, Indian, Caribbean, south and central American ancestry. Any high-risk infant not screened at birth or for whom neonatal screening results cannot be documented should be screened for hemoglobinopathies prior to 2 months of age (37, 38, 39, 40).

Therapy

Transfusion Therapy

Transfusion therapy can prevent organ damage. The transfusion can be simple, partial exchange, and erythrocytapheresis, packed cells are the blood product of choice.

Post transfusion hematocrit of 30% and Hbs level below 30% is recommended to raise the oxygen-carrying capacity of the blood. Patients should be transfused if there is heart failure, dyspnea, hypotension, or marked fatigue, stroke, sepsis, and before surgery.

Chronic transfusion therapy may be warranted for the primary prevention of stroke recurrence, chronic debilitating pain, pulmonary hypertension, chronic renal failure, and chronic heart failure. Exchange transfusion with blood less than 5 days old help in situations requiring immediate correction of oxygen-carrying capacity without increased blood viscosity or chronic iron burden.

Pre-storage red cells leukodepletion is standard practice to reduce febrile reactions. Washed red cells should be reserved for patients who had an allergic reaction after prior transfusion, irradiated blood should be considered in patients likely to be a candidate for bone marrow transplantation (13,15,19).

Chelating Agents.

Iron overload in patients is often undetected or not treated. There is no single test to determine iron overload. Serum ferritin can be unreliable because it is an acute phase reactant and the values are often altered by inflammation, liver disease, and vitamin store.

Liver biopsy is the most accurate test for iron overload, as a noninvasive method, the superconducting quantum interference device (SQUID) is acceptable for quantitating liver iron, the best indication to begin chelating therapy is liver iron of 7 mg/g dry weight.

Pain Management

Uncomplicated acute pain is self-limited and generally lasts hours to a few days, but it can persist or recur and may migrate from one site to another. Chronic pain often is defined as pain that lasts 3 to 6 months, or more. A patient in acute pain at an emergency room usually has exhausted all home care options. Failure of home or outpatient therapy singles the need for parenteral medications.

Hematopoietic Cell Transplantation

Hematopoietic cell transplantation (HCT) has the curative potential for a board spectrum of genetic disorders, including sickle cell disease. The goal is to eliminate the sickle erythrocyte and its cellular progenitors and replace them with donor hematopoietic. Pluripotent stem cell that gives rise to erythrocytes that express no sickle hemoglobin (HbS), thereby reducing HbS levels to those associated with the trait condition.

The possibility of preventing serious complications from SCD, which can cause extensive morbidity and early death, is balanced by the risk of severe adverse events after transplantation. Nearly all transplants have utilized HLA-identical sibling donors.

The children might have a superior outcome compared to adult patients because of children's lower risk of transplant related complications such as graft-versus host disease and because of a presumed lower burden of sickle-related organ damage. The results of transplantation are best when performed in children with a sibling donor who is HLA- identical children with SCD who experience significant, noninfectious complications caused by vaso-occlusion should be considered for HCT (15, 52, 53, 54).

Patients and Methods

This study examined three different perspectives. Information utilized in this study was initially collected, retrospectively, through Hematology Clinic records and was refined prospectively with data collected from the patients during visits in the last 5 months. The files for 40 patients who attended the hematology clinic in the last 5 years were also analyzed to complete our data. The focus of this study was concentrated on the geographical location to see the distribution of hemoglobinopathies in different regions of the country, the nationality of the patients, their race, age at the time of the study and at diagnosis, parents' consanguinity, and school performance. There was also a full clinical examination conducted for all systems at the last visit including hepatosplenomegaly, cardiovascular, legs (for ulcers), anthropometric measurements for patients more than 2 years of age, bone age, results for the investigation, especially MCV, MCHC, retics, Hb electrophoresis. An ultrasound of the abdomen was conducted to assess the presence/absence of gallstones. A chest x-ray was conducted to rule in/out the presence of cardiomegaly. Screening of family members was also conducted to see the number of heterozygotes and homozygotes within various families, clinical course of the disease and its complications, a number of admissions for each patient and the modality of therapy received.

Results

Figure 1 represents a total of 16 families with 78 children with hemoglobinopathies, SCA 58 (74.4%), SCT 13, (16.7%), hemoglobin C trait 2 (2.26%).

Fig-1: Types of hemoglobine

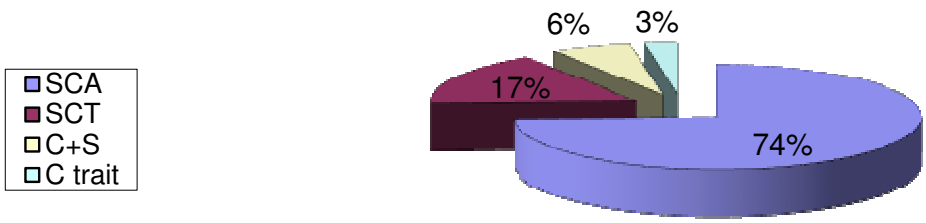
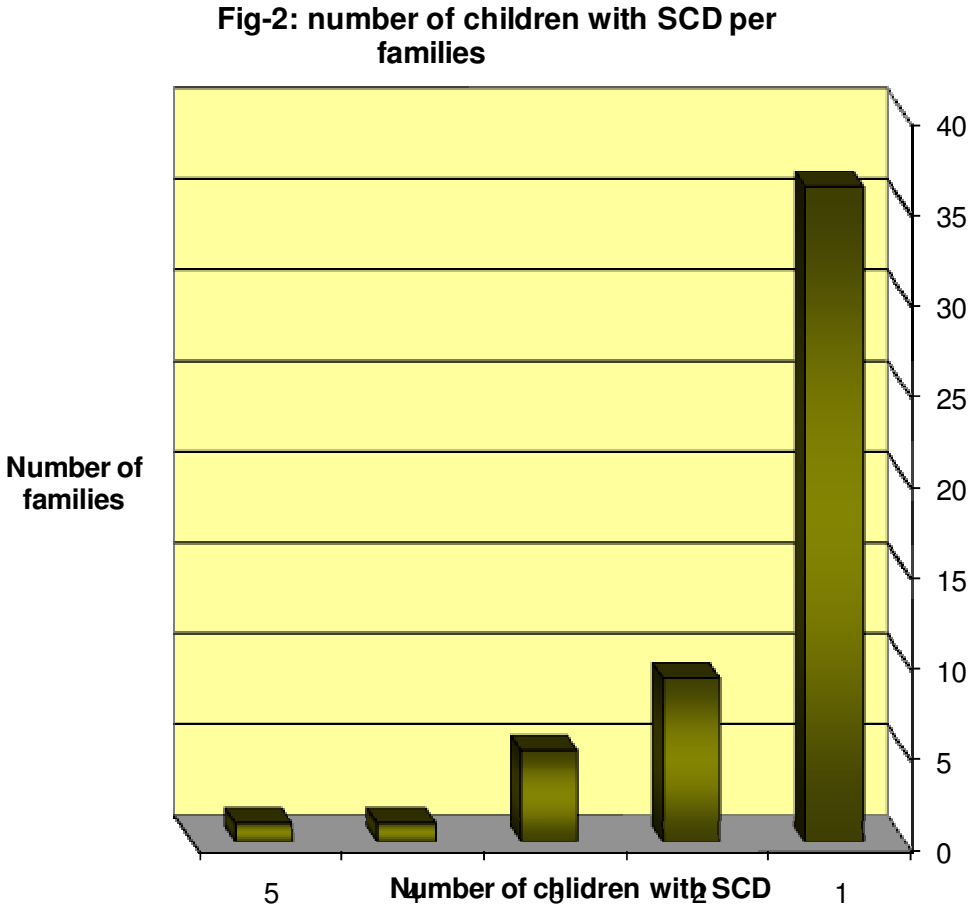


Figure 2 represents the number of children affected in each family, ranging from 1-5.



Approximately, hemoglobinopathies were seen in 18.1% from the total cases (430) in the clinic. The ages at the time of evaluation, ranged from 6 months to 26 years, with a mean of 10.84 years ± 6.75 years. At the time of diagnosis, the ages ranged from birth to 8 years, with a median of 9 months.

Table (1): Nationality of the patients (n = 78) with sickle cell disease.

Nationality	Number of cases	%
Libyan	56	72
Sudanese	11	14
Chadian	6	7.6
Palestinian	5	6.4

Table 1 represents the breakdown of patients, based on nationality. All Libyan patients (72%) were of African descent and the remainder from Chad, Sudan and other neighboring countries.

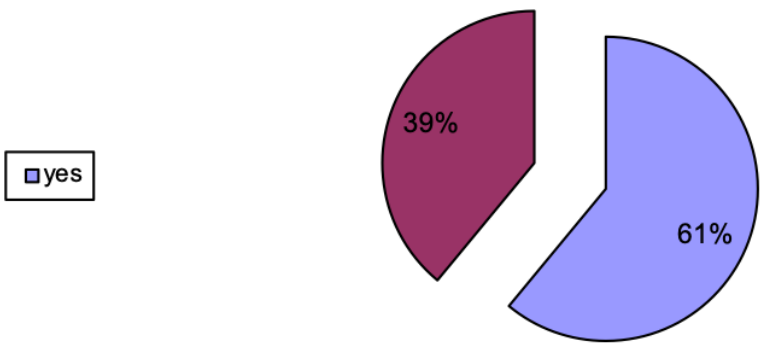
Table 2 presents with a breakdown of the patients, based on their current residential location.

Table (2): Residence of the patients (n = 78) with sickle cell disease.

Residence	No	%
Benghazi and its periphery.	40	51.3
Derna	6	7.7
Ejdabia	1	1.3
South areas	1	1.3
Tubrek	30	38.5

Despite 51.3% of the patients living in, or around, Benghazi, Libya (51.3%), the patients were originally from the south areas.

Fig-3: Consanguinity



Amongst the patients, there was a male to female ratio of 1:1.4. 61% of the families are 1st degree relatives (consanguinity), as presented by Figure 3.

40 patients were admitted on 107 occasions during the past 5-year period, with anemia being the main sign of presentation upon admission. As depicted in Table 3, 65% of admissions were due to severe anemia, 20% due to a vaso-occlusive crisis, 25% to an infection and 3% due to splenectomy. It is important to note that within this 5-year period of admissions, there was an overlap for causes of admission.

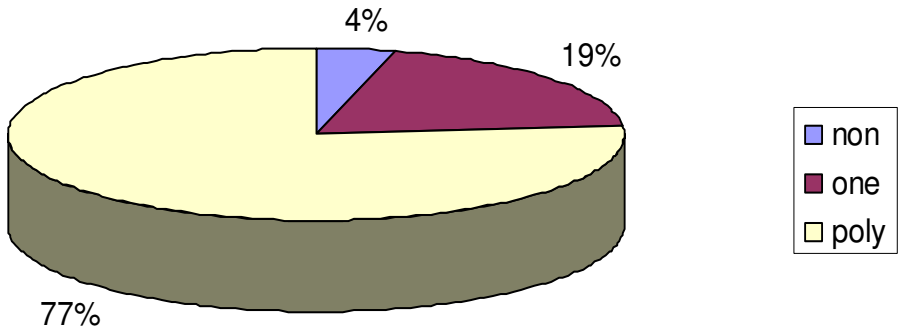
Table (3): **Morbidity profile of 40 Patients Admitted on 107 Occasions.**

Causes of admission	No of admission
Severe anemia	65
Vaso.occlusive crisis	20
Infection	25
Splenectomy	3

NB: These admissions in 5-year period, there is an overlap for causes of admission.

The number of admissions for each patient ranged anywhere from 1 to 10 times, with a mean of 2.6. The frequency of blood transfusions ranged anywhere from 0 to 10 times, with a mean of 3 times, as depicted in Figure 4.

Fig- 4: Number of blood transfusion



The complications ranged from mchol elithiasis (4.8%), stroke (9.5%), he patitis B and C (9.5%) to acute chest syndrome (6.3%) and 1.2 patients whom died from overwhelming sepsis, post splenectomy syndrome within a 6 months period. This data is illustrated in Table 4.

Table (4): Complications of the patients (n=63) with Sickle Cell Disease$^{\chi}$.

Complication	No of the patients	%
Stroke	6	9.5
Gallbladder stone	3	4.8
Hypersplenism	4	6.3
Acute chest syndrome	4	6.3
Hepatitis (B&C)	6	9.5
HIV	2	3.1
Post splenectomy syndrome	1	1.5
Total	26	39

χ It include patients with Hbss and Hb sc (symptomatic patients only)

Table (5): Treatment modality of the patients (n=63) with Sickle Cell Disease.

Type of therapy	No of the patients	%
Blood transfusion	60	96%
Folic acid	60	96%
Antibiotic	60	96%
Splenectomy	3	4.8%
Pneumovax	3	7.9%

NB: All patients who pass 1st year of life are treated with blood transfusion, folic acid and penicillin 96% of the patients are treated with blood transfusion and antibiotics, as depicted in Table 5.

Table 6 shows clinical data and the investigation of the patients. Adolescent growth spurt is delayed below the mean for the height.

Table (6): Clinical and laboratory results of patients (n=63) with SCD.

	No. of the patients	%
A) Clinical Examinations		
Hepatomegally	63	100 %
Splenomegally	19	30.2 %
Icterus	63	100%
Anemia	63	100 %
B) Laboratory results		
Hb		
5-7 g/L	55	87 %
≥ 8 g/L	8	13 %
MCV		
< 83 fl	25	40 %
≥ 83 fl	38	60 %
MCHC		
< 32 g/dl	21	33 %
≥ 32 g/dl	42	67 %
HbS		
≤ 80 %	0	0
≥ 80 – 100 %	63	100%
Retics		
≤ 5 %	5	8 %
≥ 5%	58	92 %

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Table 7 presents with information in regard to growth and development of patients more than 2 years of age; skeletal maturation is delayed 1 year below their chronological age.

Table (7): Anthropometric measurements for patients (n=48) with Sickle Cell Disease.

	NO. OF THE PATIENTS	%
Weight		
≤5th percentile	35	73%
10th percentile	9	18.2 %
25th percentile	4	9 %
≥50 percentile	0	0%
Weight		
At percentile	5	10 %
At 25th percentile	10	20 %
≥ 50 percentile	33	70 %

Discussion

The frequency of hemoglobin variants in the Arabian Peninsula is amongst the highest in the world, where the prevalence of sickle cell disease is 2.7/1,000 live births in 1989-1992 (6, 14). It is as high as 25-30% in western Africa where 8-10% of the newborns are born with sickle cell disease (12, 13). Libya is a large country with varying environmental, social, genetic and demographic factors among its different regions, which require a lot of examination to see the pattern of the disease in different regions of the country. Doing so, however, allows us to understand that the disease is not uniformly distributed in Libya and the majority of the cases are isolated to being from the South, making it difficult to estimate the prevalence of the disease. Sickle cell disease is common in the southern regions of Libya, but this is only a small sample of our study. Our study represents only a small sample from the total case and concentrates on symptomatic patients who live in Benghazi, Libya.

Sickle cell disease is inherited from parents carrying the sickling disorder, which increases by consanguineous marriage (1, 2, 4). In our study, 60% of the parents were 1st-degree relatives.

Early diagnosis amongst the parents who want to marry is the key to prevention. The screening test for SCD has been started in Iran, the Arabian Peninsula, Oman, and a few countries in Africa for some years now (7, 8, 9, 10, 11).

To define the morbidity profile of sickle cell disease in Libyan children, we analyzed data from 40 children that were admitted on 107 occasions for 5 years, with the number of admissions ranging from 1-10 times in the 5-year period. As mentioned previously anemia was the main cause of admission, seen in 60% of the admissions amongst the 40 children. The opposite findings were present in Omani children where 83% of the admissions were due to a vaso-occlusive crisis, followed by anemia at 12% and infection at 4% (10, 11, 14). In comparison with other studies, the complication of the disease is low, where we have only 9% of our patients with a stroke while other studies noted stroke being a complication within 25% of their patients (21, 22, 23, 25). About 10% of the strokes occurring in Saudi children were due to SCD (14). Gallbladder stones were found in 4.8% of our patients while it is as high as 70% in other studies (18, 20). Hepatitis B and C positivity were found to be 2.5 and respectively 12.6% in other studies (20, 45, 47), which was nearly equivalent to ours as we have Hepatitis B at 1.5% and Hepatitis C at 8% in our study. Most of our patients also had poor performance in school academics due to suffering from chronic pain which was moderate in severity and the anemia that affected their school attendance.

By the age of 2, children with sickle cell disease have been detected with growth retardation which affects weight more than the height (3, 4, 13). These findings are similar to ours where about 73% of our patients weighed in the 5th percentile. Only 10% of the patients had their height in <10th percentile and 70% had their height in the ³ 50th percentile. Skeletal maturation is also delayed, and it is relayed to the degree of hemolysis. There have been reports of responses to folic acid and zinc supplementation (50, 56), but these approaches are not recommended as standard care. In all our cases, the bone age of these children was below their chronological age. Hydroxyurea is a valuable adjunct in the treatment of severe SCD, although its clinical effectiveness for individuals with SCD has not yet been reported (45, 47). Our patients refused to be treated by hydroxyurea.

Conclusion

In conclusion, sickle cell disease is common in Libya, but this study was not sufficient for evaluation of the disease as only a small sample was studied. Also, this disease is not uniformly distributed in Libya and most of the cases were from the southern areas. Most of the cases of sickle cell disease were also amongst the African descents. Patients that we're able to pass the 1st decade of life had learning disabilities. Weight was more affected than height by sickle cell disease. Patients are also poorly managed when it comes to chronic pain that comes with having sickle cell disease. There are several methods through were sickle cell disease could be maintained or caught early in life. Firstly, there needs to be health education to increase awareness of the disease, in general. Doing so would allow the community to be aware of the signs and symptoms to be aware of when it comes to the notion of what sickle cell disease consists of. Secondly, because sickle cell disease is most commonly seen in 1st-degree relatives that choose to engage in marriage, there needs to be a screen that is done amongst the parents to ensure that neither of the two individuals is carriers of sickle cell. Previous knowledge of who is a carrier and who is not would allow for precautions to be taken right from birth, therefore, decreasing the time of diagnosis. In terms of the optimal management modalities, further studies need to be conducted to ensure what management options are present, especially the psychosocial.

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