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Prevalence of Thalassemia and Sickle Cell Anemia according to the Statistics of the Center for the Care of Patients with Thalassemia and Genetic Blood Disorders in Sana'a, Yemen 2018

A research submitted in partial fulfillment for the requirement of the Diploma Degree in laboratory

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الجمهورية اليمنية
وزارة التعليم الفني والتدريب المهني
الكلية الالمانية للعلوم الطبية والتقنية
قسم المختبرات

معدل انتشار الثلاسيميا والانيميا المنجلية حسب احصائيات مركز رعاية أمراض الثلاسيميا و الدم الوراثية صنعاء اليمن ٢٠١٨

بحث مقدم الى قسم المختبرات – الكلية الالمانية للعلوم الطيبة والتقنية
كاستيفاء جزئي للحصول على درجة الدبلوم في مجال المختبرات

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٢٠١٩

إهداء...

إلى ذلك القلب النابض بالحياة إلى أبائنا وأمهاتنا الغاليين

شكرنا لا يمثل شيئاً أمام عطفكم وحنانكم ودعمكم وحبكم لنا

لكن واجبنا يحتم علينا شكركم والدعاء لكم دائما ،،،

إلى كل من مدَ إلينا يد العون والحب والعطاء إلى دكتورتنا الغالية

د/ رانيا توفيق الاثوري

الى الجمعية اليمنية لمرضى الثلاسيميا وامراض الدم الوراثي

نوجه لكم تحية شكر وإجلال وبرقية تقدير وعرفان لما تقدموه من جهود مبذولة تجاه مرضى الثلاسيميا وامراض الدم الوراثي ونشد على ايديكم وصبركم وعزيمتكم ونسأل الله ان يجعل اعمالكم خالصة لوجة الكريم ويكتب لكم كل الأجر

والشكر الجزيل موصول لمن ساعدنا في تحليل النتائج د . إدريس الميدان

Contents :

LIST OF ABBREVIATION

Hb-S : Hemoglobin S

SCD : Sickle Cell Disease

SCA : Sickle Cell Anemia

Hb-H : Hemoglobin H

Hb-F : Hemoglobin F

CD : Cluster of Differentiation

NSAIDs : Nonsteroidal Anti-inflammatory Drugs

ACS : Acute Chest Syndrome

G6PD : Glucose 6 Phosphate Dehydrogenase

Hb : Hemoglobin

MCV : Mean Corpuscular Volume

fL : Femto Liter

MCH : Mean Corpuscular Hemoglobin

IDA : Iron Deficiency Anemia

RDW : Red Cell Distribution Width

RBC : Red Blood Cell

HPLC : High Performance Liquid Chromatography

FDA : Food and Drug Administration

DF : Desferrioxamine

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Abstract

Sickle cell disease/anemia and thalassemia are hemoglobinopathies cause by inherited abnormal gene or absent or decrease of globin chain of hemoglobin structure, this study aimed to determine the prevalence of thalassemia and sickle cell anemia in Sana'a, Yemen 2018. And determine association between prevalence the thalassemia and sickle cell anemia with education of family and kinship relationship between parents. A retrospective study based on data collected during the period (2018) for the Thalassemia and genetic blood diseases cases recorded in Sana'a city by Statistics the Center for the Care of Patients with Thalassemia and Genetic Blood Disorders. The total number of cases of Thalassemia and genetic blood diseases was 325 in 2018 where number of thalassemia (minor, major) cases were 51 cases and sickle cell diseases and sickle cell trait cases were 259 cases and G6PD was 14 cases. Number of thalassemia and genetic blood diseases cases who them parents have kinship relationship was 175 cases but without kinship relationship was 140 cases. Number of educated fathers that have infected childern with thalassemia and genetic blood diseases was 209 cases.

Finally, we recommend all body want to married to tested before marriage especially (Hb electrophoresis) to identify type and percent of hemoglobin and recommend health ministry the supporting of the Center for The Care of Patients with Thalassemia and Genetic Blood Disorders with machines and reagents for testing before marriage freely and follow up patient and provident drugs for patients freely livelong of life and deploying educations and awareness with thalassemia and genetic blood diseases.

CHAPTER 1

Introduction

1.Introduction

1.1 Incidence in the world

Sickle cell disease/anemia and thalassemia are hemoglobinopathies which are the most common monogenic diseases in the world up to 7% of the global population are carriers of an allele for an inherited hemoglobin disorder and 400,000 affected children are born each year. [(1)] The global number of neonates affected by the abnormal hemoglobin of sickle cell anemia is estimated at 5.5 million at the heterozygous state and 300,000 at the homozygous state with fulminant disease with homozygous hemoglobin S (HbS). [(2)]

80% of these are born in Sub-Saharan Africa (0.7% of local births), while the number of neonates with sickle cell anemia is estimated at 2600 for North America and 1300 for Europe. [(3)] 60,000 children are born with various forms of thalassemia for which beta thalassemia is the most common. [(4)] The original endemic areas of these diseases were overlapping and included most of Sub-Saharan Africa, the Middle East and India, with pockets in the Mediterranean area (Italy, Greece and North Africa) and Southeast Asia. [(1)] However, the disease alleles have spread all around the world because of migration. In Sweden, some 100 patients each of sickle cell anemia and thalassemia were reported between 1998 and 2003. [(5)]

We provide detailed description on national origins of sickle cell anemia and thalassemia patients diagnosed in Sweden between 1987 and 2010 based on the nationwide hospital discharge and outpatient register. At the onset, we have to emphasize that while the coverage of the diagnosed cases is likely to be close to complete, we have no information on the true incidence because there are no screening programs in place and because some mild forms of these diseases, particularly of thalassemia's, would remain undiagnosed. Yet, the medical registers show that by far the largest number of patients were immigrants and most of them originated from the endemic areas of these diseases. As some 15% of the Swedish population (total 9 million) is born outside Sweden and as many recent immigrants arrive from the endemic areas, the results highlight the need to consider national screening programs for these diseases. [(6)]

In the study of White and coworkers [7] 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 from western Saudi Arabia. [8] In the individuals with SCA, the prevalence of Xmn I polymorphic sites was reported to be similar to the prevalence reported in the south-western region of Saudi Arabia [9] and α-gene deletion occurred at a higher prevalence in patients with Yemeni SCD patients. [10]

1.2 Definition:

Normal haemoglobins are of different types in human and include Hb A, Hb A2 and Hb F. Each type of haemoglobin is a tetramer of two different globin chains, each having its own gene. The Hb A ($2\alpha2\beta$) is almost 95-97 %, Hb A2 ($2\alpha2\delta$) is 2.5-3.5 % and Hb F ($2\alpha2\gamma$) is <1 % in adults. The α-globin gene cluster is located on the chromosome 16 while the non-α globin (β globin) gene cluster is located on the chromosome 11. Provide α and β globin polypeptides and the co-ordinated production of haem results in the formation of HbA, in normal individuals.[11]

- **Thalassemia** is inherited disorder characterized by reduced synthesis of the hemoglobin. Hemoglobin is an iron-containing oxygen transport in the red blood cells. More than 95% of normal adult hemoglobin is of HbA which consists of 2 α chains and 2 β chains. Depending upon the type of missing globin chain, it can be α-thalassemia, β-thalassemia or less common thalassemia E, thalassemia delta.[11]
- **Sickle-cell disease** is an autosomal recessive genetic disease. It is inherited from affected parents. It is a group of disorders that affects hemoglobin, the molecule in red blood cells that delivers oxygen to cells throughout the body. Normal RBCs are biconcave disc-shaped and their average lifespan is about 120 days. The lifespan of RBCs in SCD patient is only about 10 to 20 days that causes anemia. Biconcave disc shape of RBCs changes to sickle shape under low oxygen tension, which becomes stiff & sticky and tends to block the blood flow in small capillaries in SCD patients. [12]

1.3 Causes

- **Thalassemia** is due to decreased production of at least one globin polypeptide chain (beta, alpha, gamma, and delta) which results in unbalanced hemoglobin synthesis. Inheritance of thalassemia is autosomal. [13]

Beta Thalassemia results from decreased production of beta-polypeptide chains. Heterozygotes are carriers and have asymptomatic mild to moderate microcytic anemia (thalassemia minor). Homozygotes (beta-thalassemia major or Cooley's anemia) develop severe anemia and bone marrow hyperactivity. [13]

Alpha Thalassemia is a result of decreased production of alpha globin's. Heterozygotes for a single gene defect results in silent alpha thalassemia state. Heterozygotes with defects in two of the four genes result in alpha thalassemia trait, and tend to develop mild to moderate microcytic anemia but with no symptoms. Defects in three of the four genes more severely impair alpha-chain production, resulting in the formation of tetramers of excess beta chains (HbH) or, in infancy, gamma chains (Bart's Hb). Defects in all four genes are a lethal condition in utero, because hemoglobin that lacks alpha chains does not transport oxygen.[13]

- **sickle cell anemia** is caused by a point mutation in the beta globin chain, causing glutamic acid to be replaced with valine at the sixth position. HbS contains two normal alpha globin subunits and two mutant beta chains. Under low-oxygen conditions, HbS has a tendency to aggregate causing the erythrocyte to assume a sickle and become rigid, sticky and misshapen. The symptoms are characterized by chronic anemia and periodic episodes of pain. This leads to further slowing of circulation, reduction in oxygen tension. SCD inherited as autosomal recessive disorders, where carrier parents transmit the abnormal genes to the offspring. If both parents are heterozygotes for HbS, there is a 25 percent chance of having a homozygous HbSS (Sickle cell anaemia SCA) child. If one parent is a carrier for HbS and the other is carrier for one of the abnormal HbS, it results in a double heterozygote state. Heterozygotes are generally asymptomatic carriers (traits), while the SCD is expressed in the homozygotes and the double heterozygotes for two abnormal haemoglobin genes. [12]

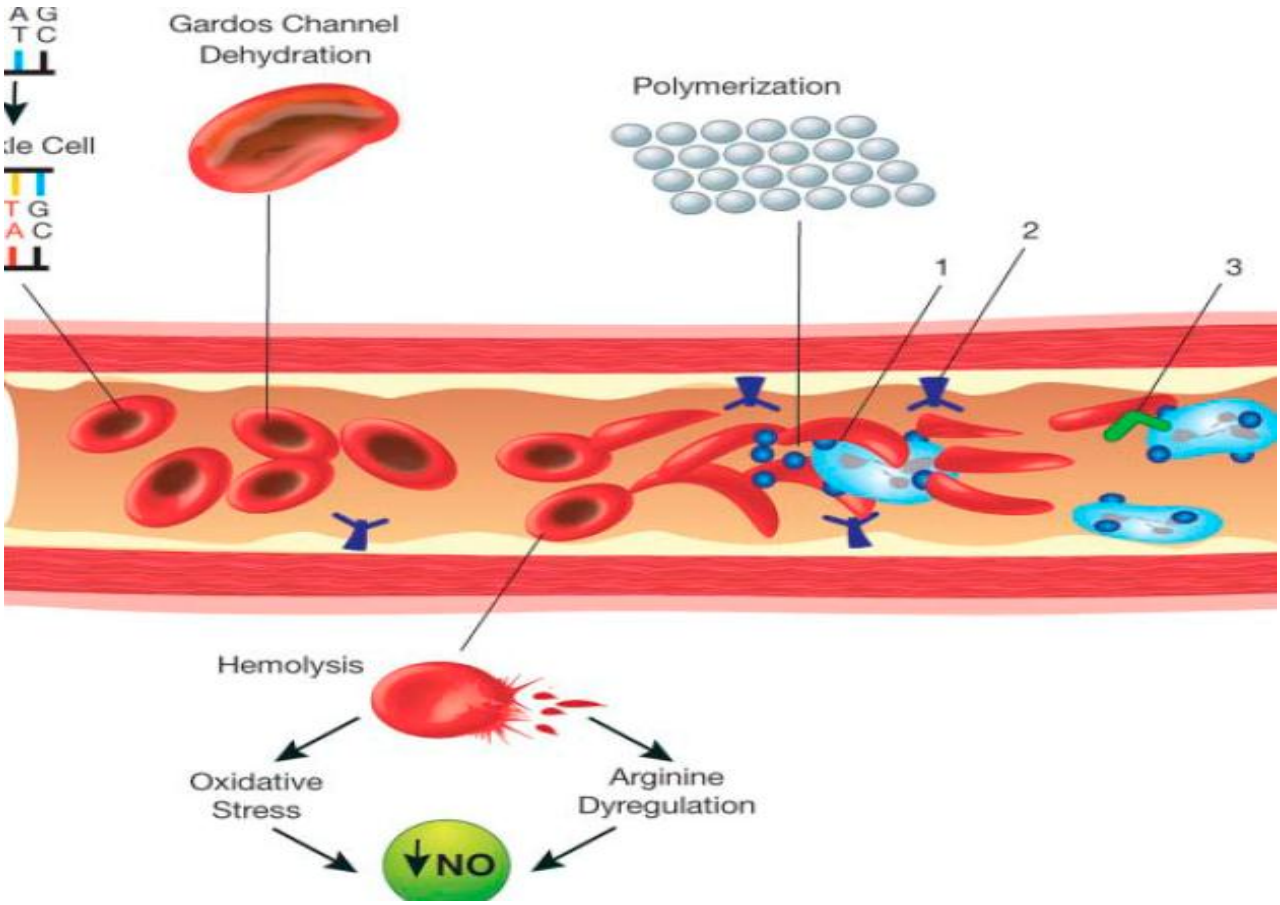

Figure 1: Schematic representation of the pathophysiology (in part) of sickle cell anemia.

A single gene mutation (GAG→GTG and CTC→CAC) results in a defective haemoglobin that when exposed to de-oxygenation (depicted in the right half of the diagram) polymerizes (upper right of the diagram), resulting in the formation of sickle cells. The disorder is also characterized by abnormal adhesive properties of sickle cells; peripheral blood mononuclear cells (depicted in light blue; shown as the large cells under the sickle cells) and platelets (depicted in dark blue; shown as the dark circular shapes on the mononuclear cells) adhere to the sickled erythrocytes. [14]

Abnormal movement or rolling and slowing of cells in the blood also can occur. These changes result in endothelial damage. The sickled red cells also become dehydrated as a result of abnormalities in the Gardos channel. Hemolysis contributes to oxidative stress and dysregulation of arginine metabolism, both of which lead to a decrease in nitric oxide that, in turn, contributes to the vasculopathy that characterizes SCD. [14]

1.4 Signs and symptoms

1.4.1 thalassemia

Some of signs and symptoms: -

1. Iron overload: People with thalassemia can get an overload of iron in their bodies, either from the disease itself or from frequent blood transfusions. Too much iron can result in damage to the heart, liver, and endocrine system, which includes glands that produce hormones that regulate processes throughout the body. The damage is characterized by excessive deposits of iron. Without adequate iron chelation therapy, almost all patients with beta-thalassemia accumulate potentially fatal iron levels.[12]

2.Infection: People with thalassemia have an increased risk of infection. This is especially true if the spleen has been removed.[12]

3.Bone deformities: Thalassemia can make the bone marrow expand, which causes bones to widen. This can result in abnormal bone structure, especially in the face and skull. Bone marrow expansion also makes bones thin and brittle, increasing the risk of broken bones.[12]

4.Enlarged spleen: The spleen aids in fighting infection and filters unwanted material, such as old or damaged blood cells. Thalassemia is often accompanied by the destruction of a large number of red blood cells and the task of removing these cells causes the spleen to enlarge. Splenomegaly can make anemia worse, and it can reduce the life of transfused red blood cells. Severe enlargement of the spleen may its removal.[15]

5. Slowed growth rates: anemia can cause a child's growth to slow. Puberty also may be delayed in children with thalassemia.[16]

6. Heart problems: Diseases, such as congestive heart failure and abnormal heart rhythms, may be associated with severe thalassemia.[17]

1.4.2 sickle cell disease

Signs of sickle cell disease usually begin in early childhood. The severity of symptoms can vary from person to person. Sickle cell disease may lead to various acute and chronic complications, several of which have a high mortality rate.[18]

1.Sickle cell crisis:

The terms "sickle cell crisis" or "sickling crisis" may be used to describe several independent acute conditions occurring in patients with SCD. SCD results in anemia and crises that could be of many types including the vaso-occlusive crisis, aplastic crisis, sequestration crisis, hemolytic crisis, and others. Most episodes of sickle cell crises last between five and seven days.[19]

a. Vaso-occlusive crisis:

The vaso-occlusive crisis is caused by sickle-shaped red blood cells that obstruct capillaries and restrict blood flow to an organ resulting in ischaemia, pain, necrosis, and often organ damage. The frequency, severity, and duration of these crises vary considerably. Painful crises are treated with hydration, analgesics, and blood transfusion; pain management requires opioid administration at regular intervals until the crisis has settled. For milder crises, a subgroup of patients manages on nonsteroidal anti-inflammatory drugs (NSAIDs) such as diclofenac or naproxen. For more severe crises, most patients require inpatient management for intravenous opioids; patient-controlled analgesia devices are commonly used in this setting. Vaso-occlusive crisis involving organs such as the penis [20] or lungs are considered an emergency and treated with red-blood cell transfusions. Incentive spirometry, a technique to encourage deep breathing to minimize the development of atelectasis, is recommended.[21]

b. Splenic sequestration crisis:

Splenic sequestration crises are acute, painful enlargements of the spleen, caused by intrasplenic trapping of red cells and resulting in a precipitous fall in haemoglobin levels with the potential for hypovolemic shock. Sequestration crises are considered an emergency. If not treated, patients may die within 1–2 hours due to circulatory failure. Management is

supportive, sometimes with blood transfusion. These crises are transient; they continue for 3–4 hours and may last for one day.[22]

c. Acute chest syndrome:

Acute chest syndrome (ACS) is defined by at least two of the following signs or symptoms: chest pain, fever, pulmonary infiltrate or focal abnormality, respiratory symptoms, or hypoxemia.[27] It is the second-most common complication and it accounts for about 25% of deaths in patients with SCD, majority of cases present with vaso-occlusive crises then they develop ACS.[23,24]

d. Aplastic crisis:

Aplastic crises are acute worsening's of the patient's baseline anemia, producing pale appearance, fast heart rate, and fatigue. This crisis is normally triggered by parvovirus B19, which directly affects production of red blood cells by invading the red cell precursors and multiplying in and destroying them.[25]

f. Haemolytic crisis:

Haemolytic crises are acute accelerated drops in haemoglobin level. The red blood cells break down at a faster rate. This is particularly common in patients with coexistent G6PD deficiency. Management is supportive, sometimes with blood transfusions.[25]

1.5 Diagnosis

1.5.1 diagnosis of thalassemia

complete blood count (CBC) and blood film :-

Both α- or β-thalassemia carriers (heterozygotes) present with microcytic hypochromic parameters with or without anemia, which requires a differential diagnosis to exclude iron-deficient anemia. Family history and ethnicity may provide useful information in approaching the laboratory diagnosis of thalassemia. The hematological parameters including

red cell indices and morphology, followed by separation and measurement of Hb fractions are the basis for the identification of thalassemia carrier. [26]

For screening of thalassemia, mean corpuscular volume (MCV) of less than 80 fL and/or mean corpuscular hemoglobin (MCH) value of less than 27 pg can be generally used as cutoff levels for a positive screening result.[27] The advantage of the thalassemia screening by MCV and MCH is achievement of rapid, cost effective, reproducible, and accurate results from automated hematology analyzers.

Using both MCV and MCH, the interpretation of peripheral blood smear would be considered as an important screening method for thalassemia. Typical RBC morphology in thalassemia disease consists of microcytosis, hypochromia, and anisopoikilocytosis. Microcytes can be evaluated by comparing the size of RBC with those of nucleus of small lymphocytes, and hypochromic RBCs are defined as having an increase in the diameter of central pallor of RBCs, that is, more than one-third of their diameter. Anisopoikilocytosis results from various abnormal RBC morphologies including schistocytes, microspherocytes, target cells, polychromasia, and nucleated RBCs. However, peripheral blood smear results might only suggest certain types of thalassemias from other causes of anemia, such as IDA or anemia of inflammation, and it is not possible to define a specific type of thalassemia disease based on RBC morphology only.[28]

The red cell distribution width (RDW) is a measure of the degree of variations in red cell size, and some causes of microcytic anemia, most notably IDA, are characterized by an increase in RDW. Although thalassemia produces uniform microcytic red cells without a concomitant increase in RDW, this observation is variable among the thalassemia syndromes, including notable increases in RDW in the Hb H disease and β-thalassemia minor. Therefore, the RDW may provide information that might be used as an adjunct to diagnosis but is not useful as single screening indicator. [29]

Electrophoresis including high performance liquid chromatography

In 1978, the International Committee for Standardization in Haematology has recommended laboratory tests for 3 types of laboratories.[30]

High performance liquid chromatography (HPLC) technique is a method used to separate compounds or molecules based on their chemical characteristics. Many separation principles such as size, affinity, and partition are available; for hemoglobin, ion-exchange chromatography is the most efficient and most widely used. The method can be also manually operated, but recently fully automated systems are available. Those systems may be dedicated to hemoglobin analysis; however, in low prevalence areas, the systems that can switch between glycated hemoglobin analysis for diabetes and variant hemoglobin analysis for thalassemia and hemoglobin variants may be more feasible to use. It is known to be useful for the diagnosis of β-thalassemia trait because HbA2 can be accurately quantitated.[31]

Electrophoresis

Electrophoresis is a technique used to separate molecules or compounds based on their migration pattern in a gel and electrical field. It is still widely used in clinical laboratories for protein electrophoresis and differentiation of some isoenzymes. Cellulose acetate electrophoresis is a representative custom electrophoresis technique. It is known to enable identification of Hb A, F, S/G/D, C/E, and H and other variants.[32]

Quantitative HbA_2 determination is the most valuable test for β-thalassemia carrier detection. Several methods are available: The most accurate, fast and simple are the michrochromatography and the cation exchange HPLC and capillary electrophoresis. The expected normal range for HbA_2 is between 2.4 and 3.2% in normal subject, while in typical β-thalassemia carriers, it is between 3.6 and 7%. values between 3.2 and 3.6% are considered borderline and they need further investigation, especially in young subjects or couple at risk. The normal range for HbF in adult life is usually <1.5% of total hemoglobin. [32]

Molecular characterization

α-thalassemia is caused by gene deletion in over 90% of cases. A minority of α-thalassemia cases are due to sequence variations like single nucleotide substitution, insertion, or short insertion/deletion. Gene deletion is likely due to unequal crossing between homologous regions during meiosis.[33]

Over 90% of β-thalassemia cases, as compared with α-thalassemia cases, are caused by sequence variations. More than 280 sequence variants are reported to be associated with β-thalassemia. [34]

Prenatal diagnosis

The purpose of the prenatal diagnosis is to identify and counsel asymptomatic individuals whose offspring are at risk of an inherited hemoglobinopathy and to monitor the pregnancy for complications. The clinical types of hemoglobinopathies that are targets of prenatal diagnosis are associated with potentially severe sequelae and intervene, such as sickle cell disease, β-thalassemia major resulting from homozygosity of β-thalassemia, and hemoglobin Bart's nonimmune hydrops fetalis caused by deletion or dysfunction of all 4 α-globin genes. [35] Despite the early lethality of hydrops fetalis, prenatal diagnosis is useful in this condition because a significant number of women carrying fetuses with this abnormality develop severe toxemia and severe postpartum hemorrhage. [36]

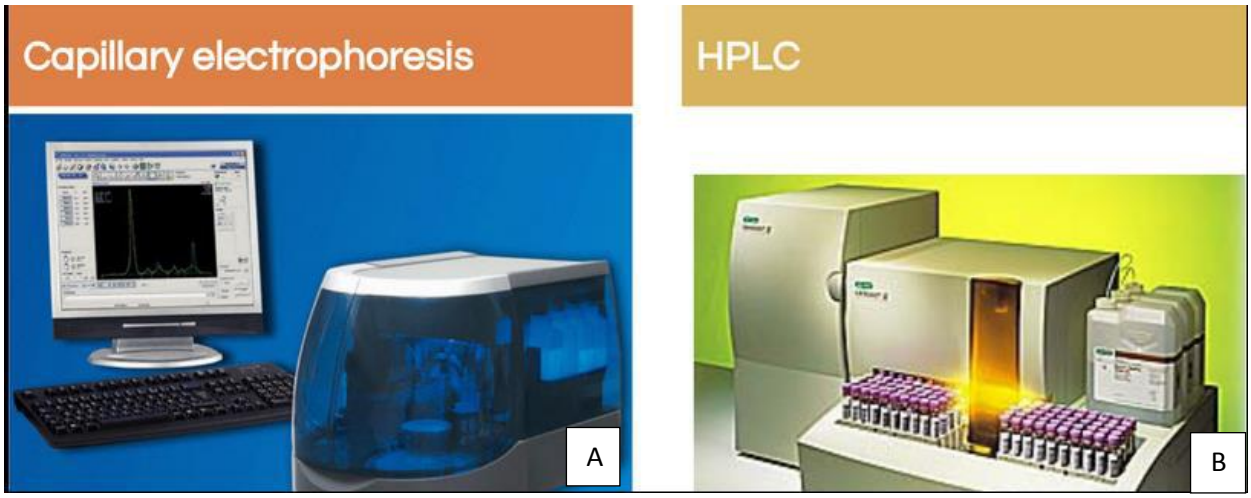

Figure 2 *:* (A) Capillary electrophoresis and (B) ion exchange chromatography used for the diagnosis of hemoglobinopathies**.** [37]

1.5.2 diagnosis of sickle cell anemia

Lab investigations for suspected SCD

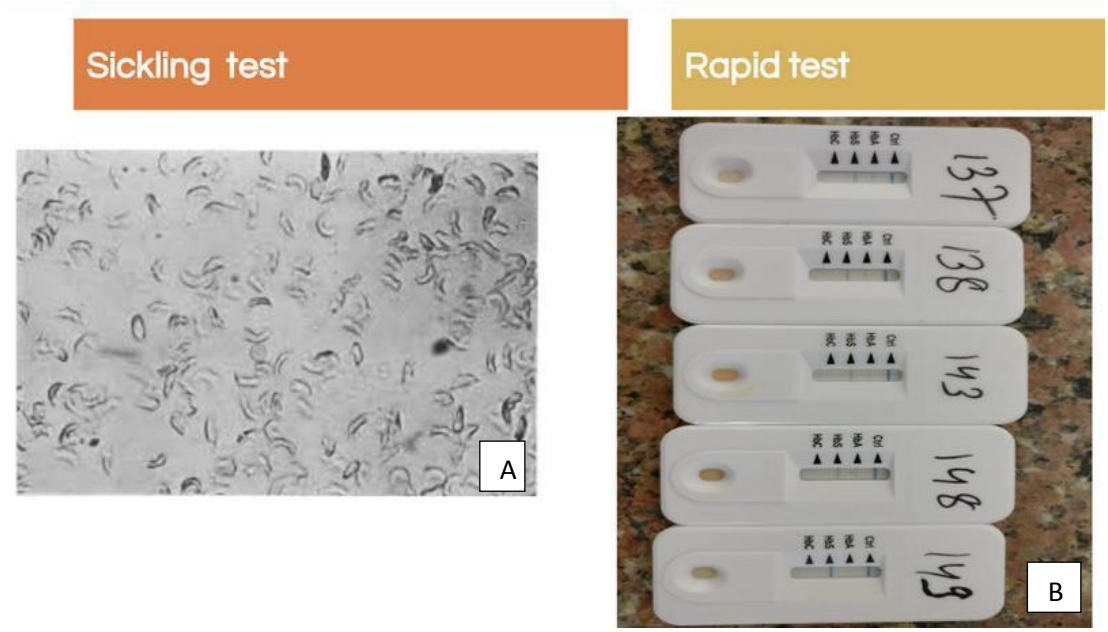

Figure 3 : Sickling test (A) and rapid diagnostic test (B) used for the diagnosis of sickle cell disease**.** [37]

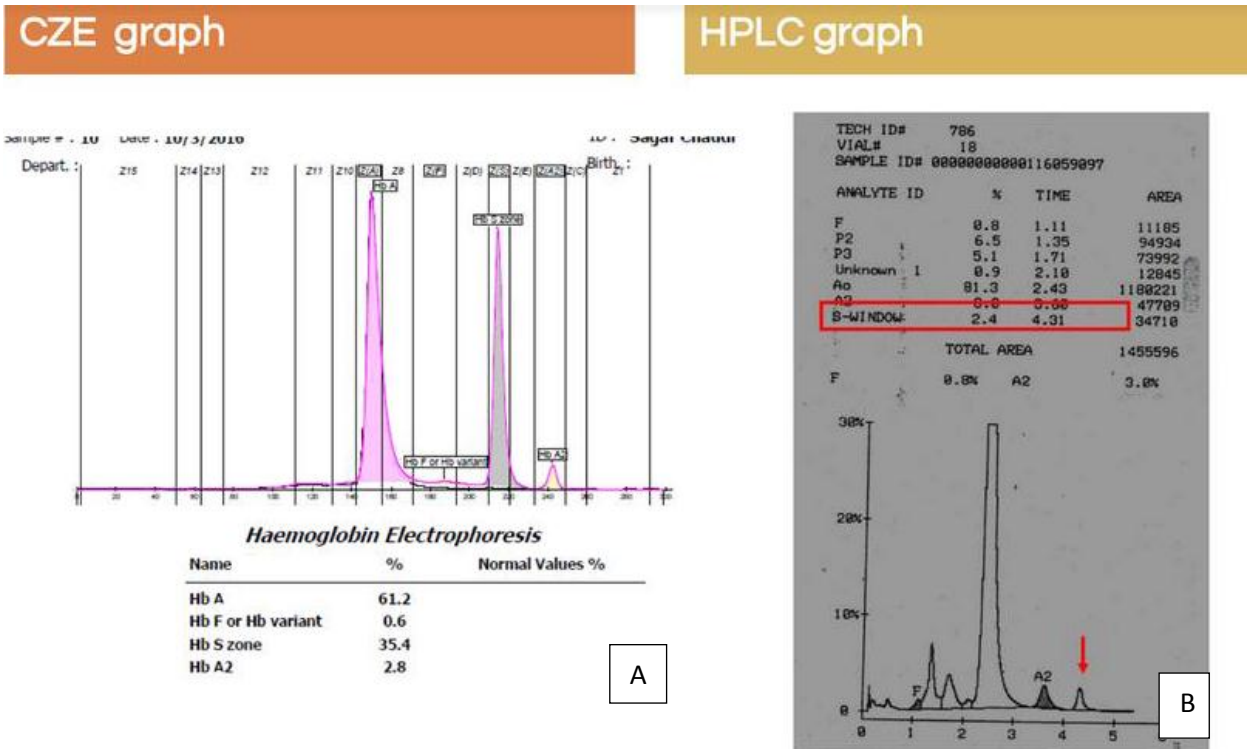

Figure 4: (A)Capillary zone electrophoresis graph showing HbA, HbF, HbS zone and HbA2 quantification. (B)HPLC graph showing interpretation of normal and abnormal Hb in patients with hemoglobinopathies**.** [37]

The complete blood count (CBC) reveals haemoglobin levels in the range of 6–8 g/dl with a high reticulocyte count (as the bone marrow compensates for the destruction of sickled cells by producing more red blood cells). [38]

A blood film may show features of hyposplenism (target cells and Howell-Jolly bodies). Sickling of the red blood cells on a blood film can be induced by the addition of sodium metabisulfite. The presence of sickle haemoglobin can also be demonstrated with the "sickle solubility test". A mixture of haemoglobin S (HbS) in a reducing solution (such as sodium dithionite) gives a turbid appearance, whereas normal Hb gives a clear solution. [38]

haemoglobin electrophoresis detect Abnormal haemoglobin forms, a form of gel electrophoresis on which the various types of haemoglobin move at varying speeds. Sickle cell haemoglobin (HbS) and haemoglobin C with sickling (HbSC)—the two most common forms—can be identified from there. The diagnosis can be confirmed with high-performance liquid chromatography. [39]

Genetic testing is rarely performed, as other investigations are highly specific for HbS and HbC.[39]

1.6 **Treatment**

1.6.1 treatment of thalassemia

1. **Blood transfusion**

Regular blood transfusion remains the main conventional treatment modality for Thalassaemia major. Before the advent of transfusion treatments in the 1960s, patients died of severe anaemia at a very early age. Patients who are poorly transfused have poor survival and high morbidity, as shown by a study in Papua New Guinea, where patients who were symptomatically anaemic, and receiving transfusion with no chelation or splenectomy, developed hypersplenism by the age of 3-4 years and usually died before they were than 9 years of age. [40]

2. Chelation therapy

Iron removal in transfusional iron overload is achieved using chelation therapy with chelating drugs like Desferrioxamine (DF) and Deferiprone (L1). Effective chelation therapy in chronically transfused patients is achieved when iron chelators remove sufficient amounts of iron, equivalent to that accumulated in the body from transfusion, to be able to maintain the body iron load at a non- toxic level. For this, chelating drugs have to be administered daily in high doses. [40]

3. Haemopoitic stem cell transplantation

Haemopoitic stem cell transplantation is the conventional curative option for Thalassaemia patients. This therapy infuses the Thalassaemic patients with stem cells harvested from a compatible donor. If engraftment occurs, these normal stem cells will then re-populate the recipient's marrow and proliferate to produce normal red blood cells. If the treatment is successful, the patient is no longer transfusion dependent. The sources of stem cells include bone marrow (compatible sibling or matched unrelated donor), cord blood (sibling or cord blood registry) and peripheral blood (sibling or unrelated donor). [41]

4. Other treatment modalities

(i) Augmentation of Fetal Hemoglobin Synthesis

(a) Hydroxyurea

Hydroxyurea is a potent ribonucleotide reductase inhibitor that is capable of inducing hemoglobin F (HbF) synthesis. [42]

(b) 5 Azacytidine

5 Azacytidine is an S-phase specific agent used as a chemotherapeutic agent for the treatment of acute myeloid leukemia. It has been shown to stimulate Hb F production in animal studies. [42]

(c) Butyrates

Butyrates have been shown to modify Hb F production in some patients. [42]

(d) Erythropoietin

This has also been used in the treatment of Thalassemia, but its high cost constraints its use on a larger scale. [42]

(e) Combination Agents

A combination of Sodium butyrate and Hydroxyurea has been used in some patients. [42]

(ii) Gene Therapy

Gene therapy remains an attractive option for patients in whom treatment with bone marrow transplantation is not possible. However, there are still many obstacles to be overcome. [41]

1.6.2 treatment of sickle cell anemia

Hydroxyurea

Hydroxyurea represents the only major breakthrough in pharmacotherapy of sickle cell disease within the past 20 years and is the only drug that is approved by the U.S, Food and Drug Administration (FDA) for treatment of adults with sickle cell disease. [43]

Glutamine

Glutamine is a conditionally essential amino acid, meaning that although the body normally makes sufficient amounts, at times of stress the body's need for glutamine increases, and in such instances, it also relies on dietary glutamine to meet this demand. The U.S. Food and Drug Administration (FDA) approved use of pharmaceutical-grade l-glutamine for sickle patients aged five years or older in July 2017. [44]

Bone Marrow Transplantation (BMT)

BMT is the only current cure for SCD and is one of the newer methods of treatments available. [45]

Iron Chelators

Red Blood Cell Transfusion deposits in the liver and heart, most commonly, resulting in end organ damage and death from liver cirrhosis or heart disease. Chronic red blood cell transfusion is utilized to suppress hemoglobin S production and is the mainstay of secondary prevention of overt stroke in patients with sickle cell disease. For the first three years after an overt stroke, the goal of red blood cell transfusions is to suppress hemoglobin S levels to 30% or less. After 3 years, the goal becomes to maintain hemoglobin S levels to 50% or less.[45]

1.7 Aim of the study

2.1. General objective

To determine the prevalence thalassemia and sickle cell anemia in Sana'a, Yemen 2018.

2.2. Specific objectives

1. To determine association between prevalence the thalassemia and sickle cell anemia with education of family.
2. To determine association between prevalence the thalassemia and sickle cell anemia with the married between of family.
3. To determine association between prevalence the thalassemia and sickle cell anemia with its distribution in cities of Yemen.

CHAPTER 2

Subject & Methods

2. Subjects and Methods:

2.1. Study area

This study was carried out in the Center of the Care of Patients with Thalassemia and Genetic Blood Disorders in Sana'a city, the capital of the Republic of Yemen.

2.2. Study population

The study was included patients of thalassemia and sickle cell anemia who came from different areas of Yemen to the Center for The Care of Patients with Thalassemia and Genetic Blood Disorders in Sana'a city –Yemen.

2.3. Study design

This study was a retrospective study

2.3.1. Inclusion criteria

- Any child infects with thalassemia and sickle cell anemia in the Center for The Care of Patients with Thalassemia and Genetic Blood Disorders.

2.3.2. Exclusion criteria

- Any child doesn't infect with thalassemia and sickle cell anemia.

2.4. Data collection

This was a retrospective study based on data collected during the period 2018 for the thalassemia and sickle cell anemia cases recorded in Sana'a city by old Registers and a administered structured questionnaire was used to collect socio-demographic data. The data collected from the Center for The Care of Patients with Thalassemia and Genetic Blood Disorders.

2.5 Statistical analysis

Data coded and entered into the computer to the statistical program and presented as mean, standard deviation, percentages, tabulation or graphical representation required. Chi square test used for categorical variables and student's t-test for continuous variables. All statistical analyses performed using the Statistical Package for Social Science (SPSS) version 24.

CHAPTER 3

Results AND Discussion

3.1 Results

3.1.1 Result of Hb electrophorsis in infected childern with thalassemia and genetic blood diseases

Table.1 Number and percent of sickle cell trait, sickle cell anemia, minor thalassemia, major thalassemia and G6PD cases in 2018 according to the Center for The Care of Patients with Thalassemia and Genetic Blood Disorders

	Hb results	Frequency	Percent
	< 50% HbS (sickle cell trait)	21	6.5
	>= 50% HbS (sickle cell disease)	238	73.2
	> 3.8% HBA2+HBA (minor thalassemia)	3	0.6
	HBA+HBF+HBA2 (major thalassemia)	49	15.1
	G6PD	14	4.3
	Total	325	100.0

prevalence of sickle cell disease cases was the highest cases in 2018 which was 73.2% and minor thalassemia cases was the lowest cases in 2018 which was 0.6 % .

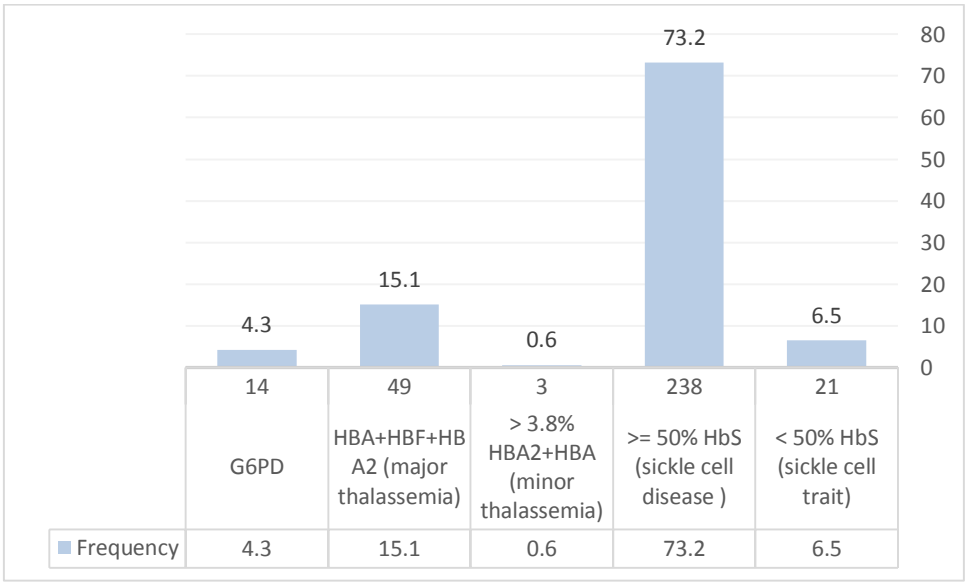

Figure 5 : Explanation histogram for distribution of sickle cell trait , sickle cell anemia , minor thalassemia , major thalassemia and G6PD cases in 2018 according to the Center for The Care of Patients with Thalassemia and Genetic Blood Disorders

3.1.2 Result of age grades in infected childern with thalassemia and genetic blood diseases

table.2 Number and percent of infected with thalassemia and genetic blood diseases less than and equal five old age and between six to eleven old age and more than and equal twelve old age in 2018.

Age	No,	%
<=5	121	37.2
6-11	100	30.8
>=12	104	32.0
Total	325	100.0

Mean ±SD = (1.95±0.83)

prevalence of infected children with thalassemia and genetic blood diseases in 2018 among less than and equal five old age the highest number which was 37.2% because thalassemia and genetic blood diseases begin to appear after six months from birth.

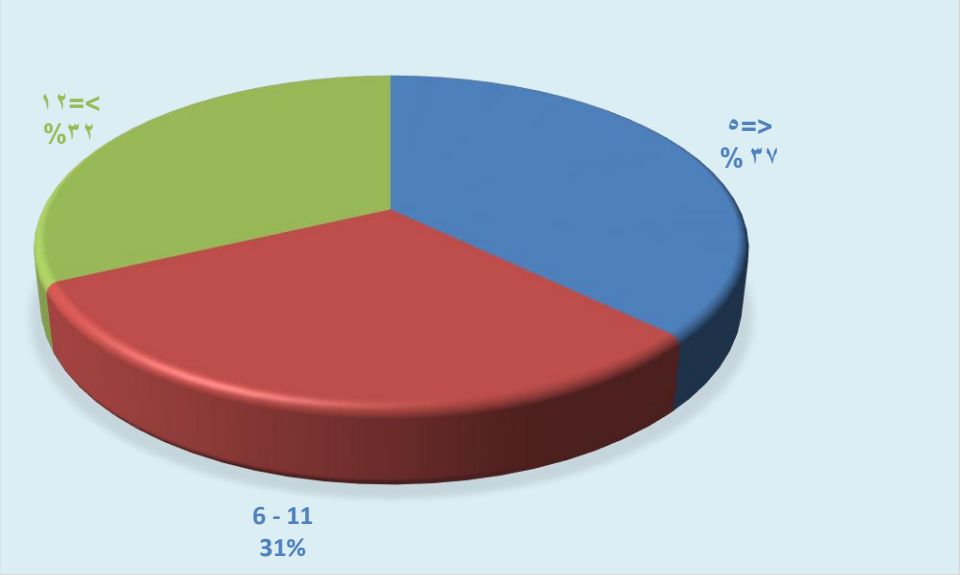

Figure 6 : Explanation histogram for age distribution of thalassemia and genetic blood diseases cases among 2018.

3.1.3 result of gender in infected childern with thalassemia and genetic blood diseases

table 3: Number and percent of sons and daughters in 2018 who infected with thalassemia and genetic blood diseases

Gender	No.	%
Male	200	61.5
Female	125	38.5
Total	325	100.0

prevalence of thalassemia and genetic blood diseases cases in female more than male where in 2018 infected male 38.5% and infected female 61.5%

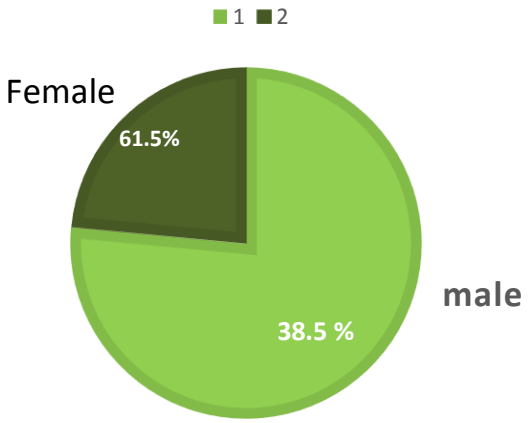

Figure 7 : Explanation histogram for prevalence of thalassemia and genetic blood diseases cases in male and female among 2018.

3.1.4 result of the education level in infected childern with thalassemia and genetic blood diseases

Table.4 Number and percent of infected childern with thalassemia and genetic blood diseases in primary, intermediate, high school and who finish school as well as non educate who stop or can't studying or less than five old age

Education level	No.	%
primary school	79	24.3
intermediate school	24	7.4
high school	42	12.9
no educate	174	53.5
finish school	6	1.8
Total	325	100.0

prevalence of non educated infected childern with thalassemia and genetic blood diseases in 2018 is very high which was 53.5% because the more cases was in less than five old age

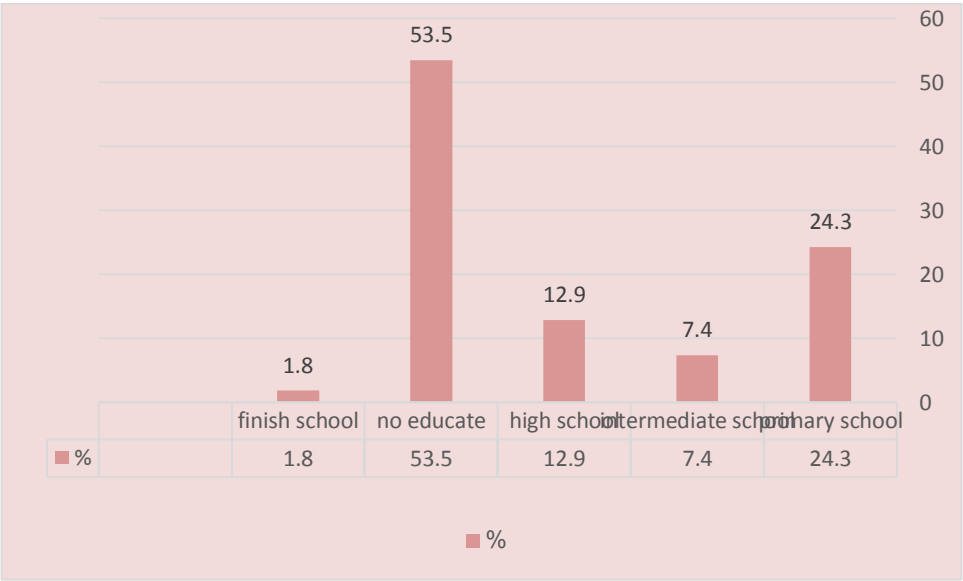

Figure 8 : Explanation histogram for percent of thalassemia and genetic blood diseases cases that study in primary , intermediate , high school and finish schools and no educate cases in 2018.

3.1.5 result of education percentage in fathers who them childern have thalassemia and genetic blood diseases

Table.5 Number and percent of educated fathers and non educated fathers in 2018 who them childern have thalassemia and genetic blood diseases

Father education	Frequency	Percent
educate	209	64.3
non educate	115	35.4
dead	1	0.3
Total	325	100.0

prevalence of educated fathers who them son and daughter have thalassemia and genetic blood diseases was 64.3% while prevalence of non educated fathers who them childern have thalassemia and genetic blood diseases was 35.4%

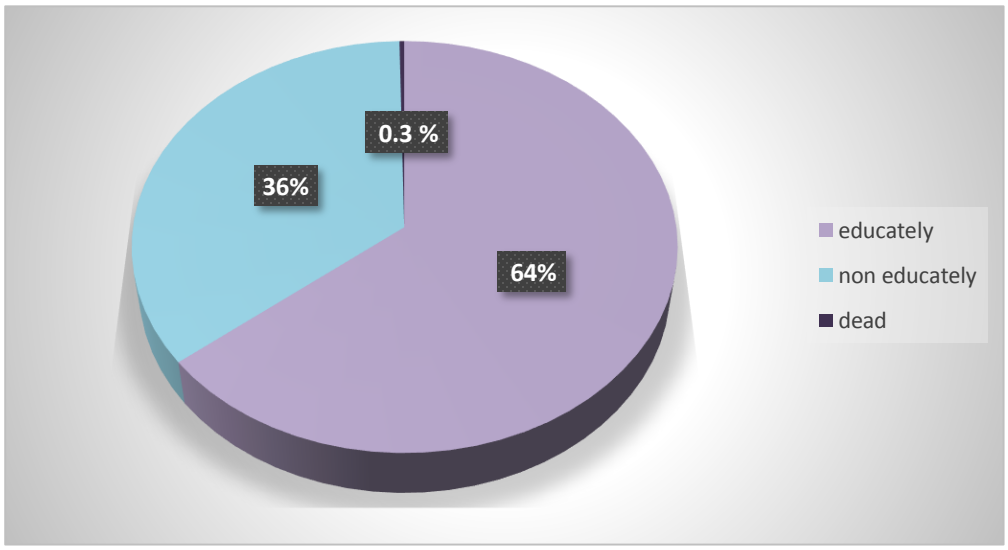

Figure 9 : Explanation histogram for percentage educated fathers and non educated fathers in 2018 who them childern have thalassemia and genetic blood diseases

3.1.6 result prevalence of education percentage in mothers who them childern have thalassemia and genetic blood diseases

Table.6 Number of educated mothers and non educated mothers in 2018 who them childern have thalassemia and genetic blood diseases

Mother education	Frequency	Percent
educate	117	36.0
non educate	207	63.7
Total	325	100.0

prevalence of non educated mothers who them childern have thalassemia and genetic blood diseases was higher in 2018 which was 63.7% while educated mothers who them childern have thalassemia and genetic blood diseases was 36.0%.

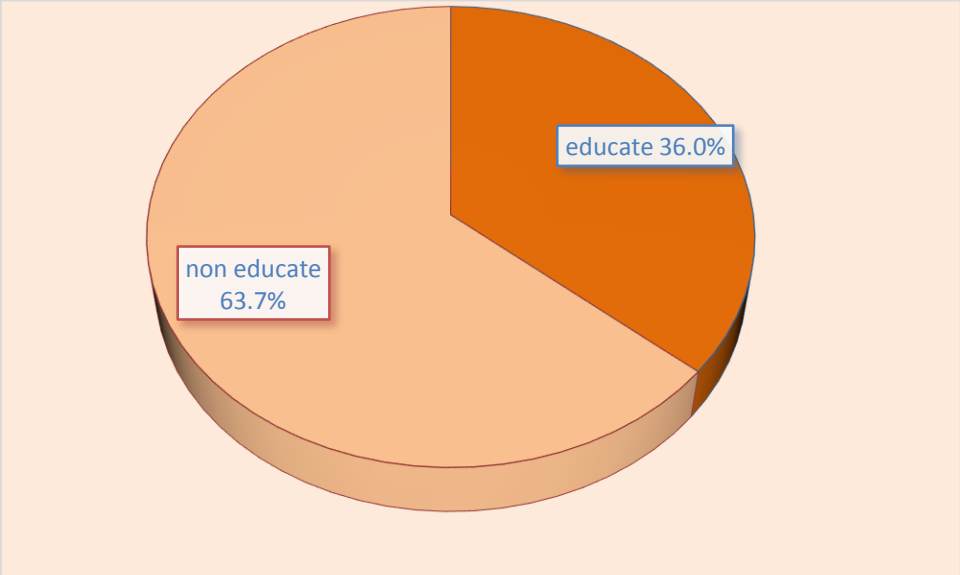

Figure 10 : Explanation histogram for percentage educated mothers and non educated mothers in 2018 who them childern have thalassemia and genetic blood diseases

3.1.7 result of repeated number of thalassemia and genetic blood diseases in family

Table.7 Number of one infected childern with thalassemia and genetic blood diseases in family and more than one infected childern with thalassemia and genetic blood diseases in family in 2018.

REPEAT	Frequency	Percent
1	249	73.5
>1	76	21.2
Total	325	100.0

Mean ±SD =
1.32 ±0.57

Prevalence of one infected childern with thalassemia and genetic blood diseases in family in 2018 was 73.5% and Prevalence of more than one infected childern with thalassemia and genetic blood diseases in family in 2018 was 21.2% .

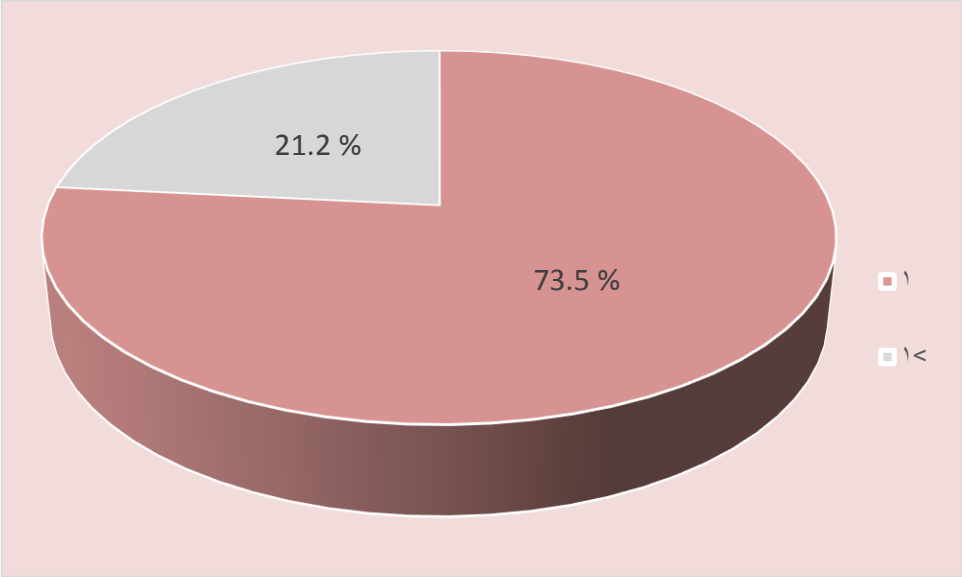

Figure 11 : Explanation histogram for percentage number of infected childern with thalassemia and genetic blood diseases in the same family (one or more than one) in 2018

3.1.8 result of kinship of parents in family who them childern infected with thalassemia and genetic blood diseases

Table.8 Number and percent of kinship between parent that have infected childern with thalassemia and genetic blood diseases in 2018

Kinship	Frequency	Percent
yes	175	53.8
no	148	45.5
non available	2	0.6
Total	325	100.0

Prevalence of thalassemia and genetic blood diseases in family with kinship relationship was 53.8 % in 2018 while Prevalence of thalassemia and genetic blood diseases in family without kinship relationship was 45.5% in 2018.

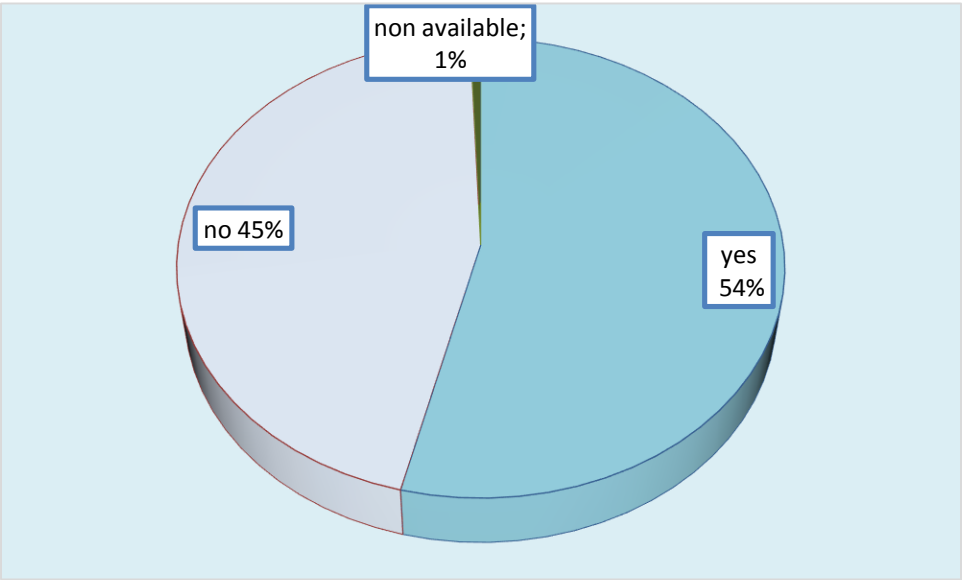

Figure 12 : Explanation histogram for prevalence of thalassemia and genetic blood diseases in family with kinship relationship and without kinship relationship in 2018

3.1.9 result of address of infected childern with thalassemia and genetic blood diseases in Yemen

Table.9 number and percent of infected childern with thalassemia and genetic blood diseases in cities of Yemen in 2018

address	Frequency	Percent
Sana a	97	29.8
taiz	48	14.8
hajjah	61	18.8
ibb	11	3.4
almahwait	10	3.1
saada	5	1.5
dhamar	25	7.7
aljawf	2	0.6
shabwah	1	0.3
alhudida	33	10.2
rema	6	1.8
mareb	1	0.3
lahj	3	0.9
AMRAN	15	4.6
another country	2	0.6
aldalaa	3	0.9
adan	2	0.6
Total	325	100.0

Mean ±SD =
1.32 ±0.57

Prevalence of thalassemia and genetic blood diseases in Sana'a city in 2018 was the highest which was 29.8 % because collect the data from to the Center for The Care of Patients with Thalassemia and Genetic Blood Disorders, Sana'a then the second prevalence in Hajjah was 18.8 % then Taiz was 14.8 %, the lowest prevalence in Yemen in 2018 was in Mareb and Shabwah was 0.3 %.

Place	Hb result					Total
	< 50 % Hb S (sickle cell trait)	>= 50 %Hb S(sickle cell disease)	> 3.8 %HBA2+HBA (minor thalassemia)	HBA+HBF+HB A2 (major thalassemia)	G6PD	
sanaa	4	67	2	14	9	97
taiz	2	43	0	2	1	48
hajjah	6	44	0	9	2	61
ibb	1	7	0	3	0	11
almahwait	1	7	0	2	0	10
saada	0	5	0	0	0	5
dhamar	3	18	0	3	1	25
aljawf	0	0	0	2	0	2
shabwah	0	0	0	1	0	1
alhudida	1	27	0	5	0	33
rema	1	4	0	1	0	6
mareb	0	0	0	1	0	1
lahj	0	3	0	0	0	3
AMRAN	1	8	0	5	1	15
another country	0	1	0	1	0	2
aldalaa	1	2	0	0	0	3
adan	0	2	0	0	0	2
Total	21	238	2	49	14	325

Table. 10 Number of cases thalassemia and sickle cell anemia in cities of Yemen in 2018.

Prevalence of thalassemia and genetic blood diseases in Sana'a city in 2018 by the Center for The Care of Patients with Thalassemia and Genetic Blood Disorders, the most cases of genetic blood diseases was sickle cell anemia which in Sana'a was 67 cases and major thalassemia was 14 cases then the second prevalence of sickle cell diseases was in Hajjah 44 cases and major thalassemia was 9 cases then in Taiz which sickle cell diseases cases was 43 cases and major thalassemia was 2 cases and after that in Al-hudidah which sickle cell diseases cases was 27 cases and major thalassemia was 5 cases.

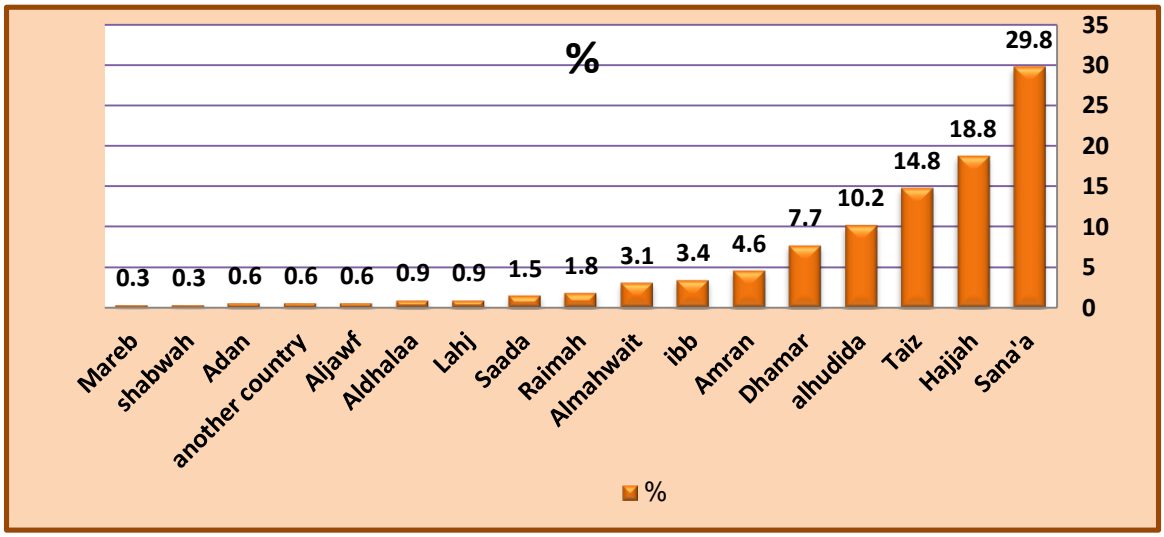

Figure 13 : Explanation for prevalence of thalassemia and genetic blood diseases in cities of Yemen according to the Center for The Care of Patients with Thalassemia and Genetic Blood Disorders, Sana'a 2018.

3.1.10 Association between education of parents and thalassemia and genetic blood diseases

Table.11 Association between Hb result in infected childern with thalassemia and sickle cell anemia and Father education

Table.12 Association between Hb result in infected childern with thalassemia and sickle cell anemia and mother education

	Test Value = 0					
	t	df	Sig. (2-tailed)	Mean Difference	95% Confidence Interval of the Difference	
					Lower	Upper
Hb-result of childern	43.744	324	.000	2.385	2.28	2.49
Father education	50.332	324	.000	1.360	1.31	1.41

	Test Value = 0					
	t	df	Sig. (2-tailed)	Mean Difference	95% Confidence Interval of the Difference	
					Lower	Upper
Hb-result of childern	43.744	324	.000	2.385	2.28	2.49
Mother education	5.852	324	.000	1.975	1.31	2.64

A highly statistically significant relationship found between Hb results in infected childern and father and mother education in our study ($p< 0.005$).

3.1.11 Association between kinship of parents and thalassemia and genetic blood diseases

Table.13 Association between Hb result in infected childern with thalassemia and sickle cell anemia and kinship of parents

One-Sample Test						
	Test Value = 0					
	t	df	Sig. (2-tailed)	Mean Difference	95% Confidence Interval of the Difference	
					Lower	Upper
Hb result in infected childern	43.744	324	.000	2.385	2.28	2.49
kinship	4.473	324	.000	2.132	1.19	3.07

A highly statistically significant relationship found between Hb results in infected childern with thalassemia and genetic blood diseases and kinship between their mother and father in our study ($p< 0.005$).

3.2 Discussion

Both sickle cell anemia and thalassemia are recessive diseases whereby both parents have to be carriers of the disease alleles for the child to be affected; 25% of children are affected by average when both parents are heterozygous carriers, they have sickle cell anemia or thalassemia trait. This is one of the reasons for the endemic presentation of these diseases in the global regions.[46] our study aimed to identify prevalence of thalassemia and sickle cell anemia in Sana'a, Yemen 2018 and determine association between prevalence the thalassemia

and sickle cell anemia with education of family and kinship relationship between parent and with its distribution in cities of Yemen.

In our result the prevalence of major and minor thalassemia cases were 15.1 % and 0.6 % and sickle cell diseases and sickle cell trait cases were 73.2 % and 6.5 % in 2018 in Sana'a, Yemen. This result was not agreed with many of studies which some studies told us that gene frequency for HbS rarely rises much above 20% – 25% of a particular population.[47] And thalassemia occur in a broad tropical belt stretching from sub-Saharan Africa through the Mediterranean regions and Middle East to the Indian subcontinent and the whole of east and southeast Asia. In this band, occurs at a frequency of 10% – 25%, although in a few localized populations such as those of north India and Papua New Guinea, they are found in up to 80% of the population. [48] And In the study of White and coworkers [(7)] the frequency of SCD in Yemen was reported as 0.95 percent.

In our study, the most common genetic blood diseases by Hb electrophorsis result in childern was Sickle cell anemia (73.2%) and the most common genetic blood diseases was in male childern (61.5%) by Hb electrophorsis result and kinship between parents who them childern have thalassemia and genetic blood disease was not necessary which parents without kinship relationship have infected childern with thalassemia and genetic blood diseases was (45.5%) and the educated fathers and mothers that have infected childern with thalassemia and genetic blood diseases were (64.3%) and (36.0%). G6PD was the lowest cases in the Center for The Care of Patients with Thalassemia and Genetic Blood Disorders in Sana'a city 2018 which was 4.3 % So, we didn't interest with studying G6PD cases in our study as we interested with studying thalassemia and sickle cell diseases.

More than one infected childern with thalassemia and sickle cell anemia inside family effect to economic of country to provide enough drugs and blood transfusion because the poverty and lack of drugs in the Center for The Care of Patients with Thalassemia and Genetic Blood Disorders or expensive of prices in pharmacy which in our study prevalence of thalassemia and sickle cell anemia in more than one inside family was 21.2 %

And distribution thalassemia and sickle cell anemia cases in cities of Yemen which the highest cases in 2018 in our study was from Sana'a city was 29.8 % then in Hajjah was 18.8 %

then Taiz was 14.8 %, the lowest prevalence in Yemen in 2018 was in Mareb and Shabwah was 0.3 %.

This study showed highly statistically significant association between infected childern with thalassemia and genetic blood diseases and kinship relationship between parents and between infected childern with thalassemia and genetic blood diseases and education of both of parents ($p< 0.005$).

CHAPTER 4

Conclusions & Recommendations

4.1 Conclusions

It is concluded that prevalence of thalassemia and genetic blood diseases in 2018 was the highest cases sickle cell diseases.

Male childern infected with thalassemia and genetic blood diseases more than female childern.

Decrease of awareness and education lead to increase of cases of thalassemia and genetic blood diseases.

By the Center for The Care of Patients with Thalassemia and Genetic Blood Disorders in Sana'a city, the more sickle cell diseases cases after Sana'a in 2018 was Hajjah and Taiz and Alhudidah, this is may be reason the gene of Hb-S present in this cities and the marriage from same family (kinship relationship) frequently.

Not necessary to infected with thalassemia and genetic blood diseases to be kinship between parents so must be all body want to married to tested before marriage (Hb electrophoresis, G6PD, Reticulocyte count) and provident this tests in all laboratories.

Must be supporting and Provident of the Center for The Care of Patients with Thalassemia and Genetic Blood Disorders with all requirements of patient from drugs and blood transfusion and tests and education.

4.2 Recommendation

1-We recommend health ministry the supporting of the Center for The Care of Patients with Thalassemia and Genetic Blood Disorders with machines and reagents for testing before marriage freely and provident drugs for patients freely livelong of life and supporting and entitlement them in all matters of them life.

2- We recommend any person want to married to tested before marriage obligatory and this tests become from condition of marriage contract and recommend all laboratories to decrease of price of tests.

3- We recommend done symposia to deploying educations and awareness in all categories of the society through different media facilities in rural and urban.

4- We recommend to done researches of hemoglobinpathies in Yemen and interest of this researches.

5- We recommend supporting and encourage diseased childern to complete his studies in school

6- We recommend to voluntary with blood to patients and provided with blood bags

7- We recommend pharmacist to non-utilizing with patients for selling drugs with expensive prices.

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Questionnaire :

Prevalence of Thalassemia and Sickle Cell Anemia according to The Statistics of The Center for The Care of Patients with Thalassemia and Genetic Blood Disorders in Sana'a, Yemen 2018 .

Part1:Demographic-characteristics-of-patients:

.Name**:** _____ No: ☐

.Address: _____ Telephone:_____

.Age:- ☐ years

.Gender:- male ☐ female ☐

. Study in school :- Primary school ☐ intermediate school ☐

high school ☐ Not educate ☐ finish school ☐

.Father's Occupation :- ☐

.Father is educated :- yes ☐ No ☐

.mather is educated :- yes ☐ No ☐

.How many of son and daugther in family affected with thalassemia and sickle cell anemia in family:- one ☐ tow ☐ More ☐

.kinship between parent :- yes ☐ No ☐

Part 2 :The result of test for Hb electrophorsis

	☐	☐	☐	☐
Son's or daughter's result	☐	☐	☐	☐
Father's result	☐	☐	☐	☐
Mather's result	☐	☐	☐	☐

خلاصة البحث بالعربى

الثلاسيميا والانيميا المنجلية عبارة عن خلل في الهيموجلوبين سببه وراثة جين غير طبيعي او غياب او نقص في سلسة الجلوبين لتركيب الهيموجلوبين ، دراستنا تهدف لتحديد انتشار الثلاسيميا والانيميا المنجلية في صنعاء اليمن لعام ٢٠١٨ وتحديد العلاقة بين الثلاسيميا والانيميا المنجلية وصلة القرابة بين الاباء وكذلك ارتباط التعليم في العائلة بكثرة انتشار المرض .

الدراسة كانت دراسة مرجعية سابقة تعتمد على تجميع بيانات مرضى الثلاسيميا وامراض الدم الوراثية في مدينة صنعاء لعام ٢٠١٨ بواسطة احصائيات مركز رعاية مرضى الثلاسيميا و الدم الوراثي .

عدد الحالات التي سجلتها المركز في عام ٢٠١٨ في المركز ٣٢٥حالة حيث عدد الثلاسيميا ٥١ حالة والانيميا المنجلية ٢٥٩ حالة وبقية الحالات كانت انيميا نقص الجلكوز ١٤ حالة .

عدد الحالات المصابة بالثلاسيميا والانيميا المنجلية التي لها صلة قرابة بين الآباء كانت ١٧٥ حالة والحالات التي ليس لها صلة قرابة بين الآباء ١٤٠ حالة. وعد الأباء المتعلمين الذي يملكون اطفال مصابين ب الثلاسيميا وامراض الدم الوراثية ٢٠٩ .

اخيرا نحن نوصي كل فرد يرد ان يتزوج عمل فحوصات ماقبل الزواج خاصة لمعرفة نوع ونسبة الهيموجلوبين الذي يملكه و نوصي وزارة الصحة بدعم مركز رعاية مرضى الثلاسيميا والدم الوراثي ب الاجهزة والمحاليل لاجل عمل الفحوصات للمقبلين ع الزواج وتوفره مجانا وكذلك متابعة حالات مرضى المركز وتزويد العلاجات للمرضى مجانا طول الحياة ونشر التعليم والوعي ب أمراض الثلاسيميا والدم الوراثي.