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Sickle cell Disease

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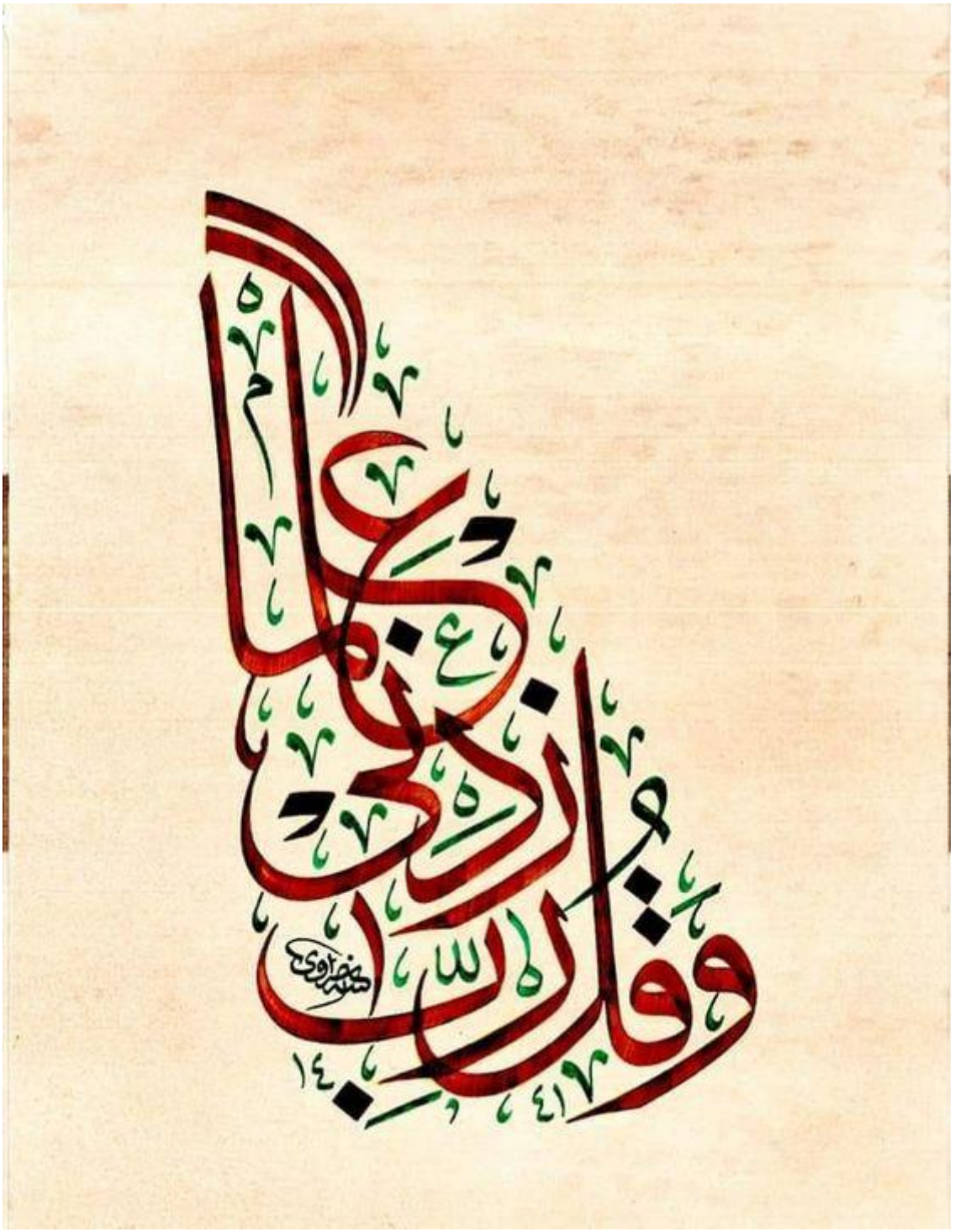
Certification of the Supervisor

I certify that this project entitled "....."
was prepared by the fifth-year student ..... under my supervision
at the College of Dentistry/University of Baghdad in partial fulfilment of the graduation
requirements for the Bachelor Degree in Dentistry.

Supervisor’s name

Date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Dedication

First of all I thank allah for the most mercy for enabling us to present this project in the best form that we wanted to be, Most of all I am thankful for my family for their endless love, assistance, support and encouragement. And for my friends for their understanding and support for us to complete this project.

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Abstract

Sickle cell disease (SCD) is the most prevalent monogenic hereditary pathology associated with the presence of hemoglobin SS in the world. It can affect individuals, leading to changes in the face and body, causing a deficiency in dental and bone tissue formation that can ultimately result in a higher level of predisposition to developing dental caries.

List of contents

List of Table

List of Figures

List of Abbreviations

SCD	Sickle cell disease
HbB	Hemoglobin b-globin gene
Hb	Hemoglobin
SC	Sickle cell anemia C-globin gene
SB	Sickle cell anemia B-globin gene
SE	Hemoglobin e-globin gene
VOC	Vaso-occlusive crisis
CBC	Complete blood count
Hb F	Fetal hemoglobin
Hb SS	Hemoglobin s-globin gene
RBC	Red blood cell

Introduction

Sickle cell disease (SCD) is a group of blood disorders typically inherited from a person's parents.[1] The most common type is known as sickle cell anaemia.[1] It results in an abnormality in the oxygen-carrying protein hemoglobin found in red blood cells.[2] This leads to a rigid, sickle-like shape under certain circumstances.[2] Problems in sickle cell disease typically begin around 5 to 6 months of age.[2] A number of health problems may develop, such as attacks of pain (known as a sickle cell crisis), anemia, swelling in the hands and feet, bacterial infections and stroke.[2] Long-term pain may develop as people get older.[2] The average life expectancy in the developed world is 40 to 60 years.[2]

Sickle cell disease occurs when a person inherits two abnormal copies of the β-globin gene (*HBB*) that makes hemoglobin, one from each parent.[4] This gene occurs in chromosome [11.][9] Several subtypes exist, depending on the exact mutation in each hemoglobin gene.[3] An attack can be set off by temperature changes, stress, dehydration, and high altitude.[3] A person with a single abnormal copy does not usually have symptoms and is said to have sickle cell trait.[3] Such people are also referred to as carriers.[6] Diagnosis is by a blood test, and some countries test all babies at birth for the disease.[5] Diagnosis is also possible during pregnancy.

The care of people with sickle cell disease may include infection prevention with vaccination and antibiotics, high fluid intake, folic acid supplementation, and pain medication. [6, 7] Other measures may include blood transfusion and the medication hydroxycarbamide (hydroxyurea).[7]

A small percentage of people can be cured by a transplant of bone marrow cells. [3]

The highest frequency of sickle cell disease is found in tropical regions, particularly sub-Saharan Africa, tribal regions of India, and the Middle East.[8] Migration of substantial populations from these high-prevalence areas to low-prevalence countries in Europe has dramatically increased in recent decades and in some European countries, sickle cell disease has now overtaken more familiar

genetic conditions such as hemophilia and cystic fibrosis.[9] In 2015, it resulted in about 114,800 deaths.[10]

Sickle cell disease occurs more commonly among people whose ancestors lived in tropical and subtropical sub-Saharan regions where malaria is or was common. Where malaria is common, carrying a single sickle cell allele (trait) confers a heterozygote advantage; humans with one of the two

alleles of sickle cell disease show less severe symptoms when infected with malaria.[11]

This condition is inherited in an autosomal recessive pattern, which means both copies of the gene in each cell have mutations. The parents each carryone copy of the mutated gene, but they typically do not show signs and symptoms of the condition. [12]

The loss of red blood cell elasticity is central to the pathophysiology of sickle cell disease. Normal red blood cells are quite elastic and have a biconcave disc shape, which allows the cells to deform to pass through capillaries. In sickle cell disease, low oxygen tension promotes red blood cell sickling and repeated episodes of sickling damage the cell membrane and decrease the cell's elasticity. These cells fail to return to normal shape when normal oxygen tension is restored. As a consequence, these rigid blood cells are unable to deform as they pass through narrow capillaries, leading to vessel occlusion and ischemia's actual anemia of the illness is caused by hemolysis, the destruction of the red cells, because of their shape. Although the bone marrow attempts to compensate by creating newred cells, it does not match the rate of destruction. [13]

Healthy red blood cells typically function for 90–120 days, but sickled cells only last 10–20 days. [13]

Aim of study

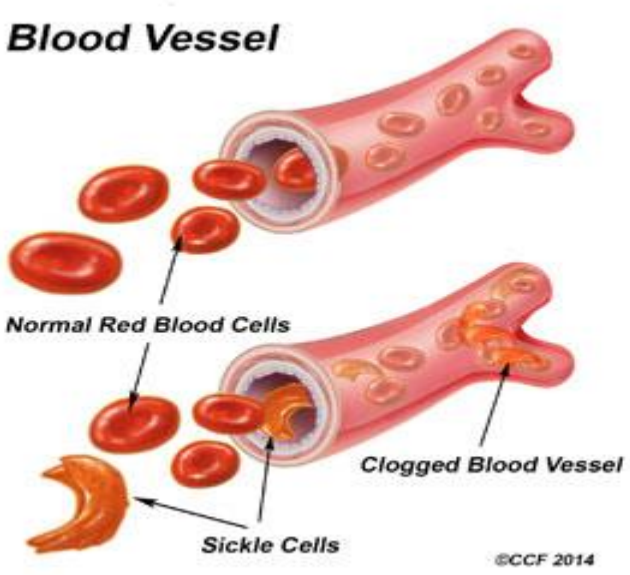
this study to review aim to know sickle cell anemia it’s epidemiology, etiology and some of oral manifestations that appear

chapter one

1.sickle cell anemia

1.1 Definition

Sickle cell anemia (SCD) an inherited disease in which the red blood cells have an abnormal crescent shape, block small blood vessels, and do not last as long as normal red blood cells. Sickle cell anemia is caused by a mutation (change) in one of the genes for hemoglobin (the substance inside red blood cells that binds to oxygen and carries it from the lungs to the tissues). It is most common in people of West and Central African descent. Also called sickle cell disease[14]



Picture 1.1 https://my.clevelandclinic.org/health/diseases/4579-sickle-cell-anemia

1.2 Epidemiology

Sickle cell anemia is a monogenic disease but presents a very complex phenotype and very variable clinical manifestations between subjects. In study, conducted on 39 patients followed at Bambino Gesù Children's Hospital, they

analyzed the main factors characterizing the pathology to assess if gender could have an influence in the clinical and therapeutic course of the disease. [14]

To the best of our knowledge scarce data are available in the literature about SCD sex differences in pediatric population. Sex hormones were recognized as responsible for gender differences in adult patients with SCD, but in the pre-puberty setting of childhood their role could be less relevant in the pathogenesis of gender differences in the pediatric population. [14]

first focus concerns the number of painful crises per year; painful

crises, in fact, in addition to being very heterogeneous, are also highly unpredictable and the few studies in literature addressing this issue speculate that the reduction of fetal hemoglobin, the increase of hematocrit and leukocyte counts, are among the parameters studied, the only ones associated with a higher rate of crisis. Moreover, an annual average of crisis between the 0.4 and the 0.8 per patient is reported, regardless of the sex of patients. [15]

the results showed that males had more episodes of painful crises per year than females, with an average higher than that reported in the literature. The reason of that difference could be attributed to the different bioavailability of nitric oxide, higher in females, as suggested in various studies. [15]

Concerning SCD clinical complications, the literature shows a greater severity of clinical manifestations in males. [15]

In a study there is a high variability in the results was noticed: the

comparison between the incidence of splenomegaly in the two groups showed no gender specificity, whereas the incidence of cholelithiasis tended to be more frequent in females, as extensively documented in literature. [15]

In the category of cardiopathies, eccentric left ventricular hypertrophy is

the most frequently reported in SCD patients. Studies showed that males are most frequently affected by this complication. Same results were already obtained by Morrison et al. at the Lady's Children's Hospital Crumlin. [15]

Concerning the incidence of vascular events, a total of two episodes was recorded

(5%), both cases in male patients. Osteomyelitis also manifested mainly in males (three episodes in males and 1 in females) confirming the tendency that males are more prone to complications than females.

Transfusions number was also analyzed. The initial hypothesis was that males needed more transfusions, as transfusions improve oxygenation and disrupt the intravascular mowing process by dilution (in the case of simple transfusion) of pathological red blood cells containing HbS. However, the results did not support this hypothesis, showing an identical average between males and females. [15]

The sample size of male patients and the fact that they had more episodes of painful/annual crises, has led us to analyze the average age to the diagnosis of the two groups: males would have an earlier diagnosis, as they have a worse clinical course than females and they need a greater number of hospitalizations and investigations.

Regarding Vaso-occlusive crises an analysis of the treatment necessary to control the pain during painful crises was performed. The pain, in the crises, is classified according to the visual analog scale (VAS) scale in mild, moderate and severe and the most recent (Italian Association of Hematology Pediatric Oncology) guidelines recommend the use of morphine in the pain control of moderate-severe crises. The analysis showed that, the percentage of severe painful crises (VAS > 6) is very similar in the two groups and, nevertheless, almost exclusively male children have needed a treatment with morphine, with. Also, this data confirms our hypothesis: males seem to have a worse clinical course than females, thus requiring more important pain therapy than females. Many studies in literature described gender differences in frequency and intensity of pain. In these studies, women often report lowerpain thresholds, higher pain ratings, and lower tolerance for pain[15].

Nevertheless, these assumptions have not been reported in SCD patients

both in adult and in pediatric populations. Since these patients experience both chronic and acute pain, there might be a long-term modulation of painsensitivity. Any differences in gender in this regard should be more thoroughly assessed in further studies. [15]

The results confirmed that gender plays a role in the pathogenesis and in the course of the disease, in particular, male gender seems to represent an indicator of a more aggressive disease course. Thus, the results showed that there is more morbidity in the male sex. This data had not yet been directly addressed in any study in the pediatric age, although it has already been shown in the adult population. The gender- specific differences observed, partly already known in the adult, have always been attributed to the hormonal changes that are physiologically present in the two sexes after puberty. However, in the pediatric population, other factors must be implicated in determining the described differences. Further studies are encouraged to highlight possible risk factors connected to gender in the SCD pediatric population. Therefore, taking these preliminary data, and their possible confirmation in wider studies, male gender could be taken into account in the initial assessment of the patients. This could, in fact, represent a simple and intuitive risk factor that could be implemented in the prognostic stratification since diagnosis, thus leading to personalized therapeutic decisions for the two sexes and the implementation of major prevention and surveillance programs for males. [15]

1.3 Etiology

Causes

Sickle cell anemia is caused by a change in the gene that tells the body to make the iron-rich compound in red blood cells called hemoglobin.

Hemoglobin enables red blood cells to carry oxygen from the lungs throughout the body. The hemoglobin associated with sickle cell anemia causes red blood cells to become rigid, sticky and misshapen.

For a child to be affected, both mother and father must carry one copy of the sickle cell gene — also known as sickle cell trait — and pass both copies of the altered form to the child.[16]

If only one parent passes the sickle cell gene to the child, that child will have the

sickle cell trait. With one typical hemoglobin gene and one altered form of the gene, people with the sickle cell trait make both typical hemoglobin and sickle cell hemoglobin.

Their blood might contain some sickle cells, but they generally don't have symptoms. They're carriers of the disease, however, which means they can pass the gene to their children.[16]

1.4 Clinical Manifestations

SCD is characterised by protean manifestations ranging from acute generalised pain to early onset

stroke, leg ulcers and the risk of premature deaths from multi-organ failure [8.] As a result of the effect

of HbF, clinical features do not begin until the middle to second part of the first year of post-natal life

when this has predominantly switched to adult haemoglobin [(47-52)]

1.5 Symptoms of sickle cell anemia

Symptoms of sickle cell anemia usually show up at a young age. They may appear in babies as early as 4 months old, but generally occur around the 6-month mark.[16]

While there are multiple types of SCD, they all have similar symptoms, which vary in severity. These include:

- excessive fatigue or irritability, from anemia
- fussiness, in babies
- bedwetting, from associated kidney problems

- jaundice, which is yellowing of the eyes and skin
- swelling and pain in hands and feet
- frequent infections
- pain in the chest, back, arms, or legs

1.6 Complications

For a baby to be born with sickle cell anemia, both parents must carry a sickle cell gene. In the United States, sickle cell anemia most commonly affects people of African, Mediterranean and Middle Eastern descent. [16]

Sickle cell anemia can lead to a host of complications, including:

- **Stroke.** Sickle cells can block blood flow to an area of the brain. Signs of stroke include seizures, weakness or numbness of the arms and legs, sudden speech difficulties, and loss of consciousness. If your child has any of these signs and symptoms, seek medical treatment immediately. A stroke can be fatal.[16]
- **Acute chest syndrome.** A lung infection or sickle cells blocking blood vessels in the lungs can cause this life-threatening complication, resulting in chest pain, fever and difficulty breathing. Itmight require emergency medical treatment.[16]
- **Pulmonary hypertension.** People with sickle cell anemia can develop high blood pressure in their lungs. This complication usually affects adults. Shortness of breath and fatigue are common symptomsof this condition, which can be fatal. [16]
- **Organ damage.** Sickle cells that block blood flow to organs deprive the affected organs of blood and oxygen. In sickle cell anemia, blood is also chronically low in oxygen. This lack of oxygen-rich blood candamage nerves and organs, including kidneys, liver and spleen, and can be fatal.[16]

- **Splenic sequestration.** A large number of sickle cells can get trapped in the spleen, causing it to enlarge and possibly causing belly pain on the left side of the body. This can be life-threatening. Parents of children with sickle cell anemia should learn to regularly feel their child's spleen for enlargement.[16]
- **Blindness.** Sickle cells can block tiny blood vessels that supply the eyes. Over time, this can lead to blindness.[16]
- **Leg ulcers.** Sickle cell anemia can cause painful open sores on the legs. [16]
- **Gallstones.** The breakdown of red blood cells produces a substance called bilirubin. A high level of bilirubin in the body can lead to gallstones.
- **Priapism.** In this condition, men with sickle cell anemia can have painful, long-lasting erections. Sickle cells can block the blood vessels in the penis, which can lead to impotence over time.
- **Deep vein thrombosis.** Sickling of red cells can cause blood clots, increasing the risk of a clot lodging in a deep vein (deep vein thrombosis) or a lung (pulmonary embolism). Either can cause serious illness or even death. [16]
- **Pregnancy complications.** Sickle cell anemia can increase the risk of high blood pressure and blood clots during pregnancy. It can also increase the risk of miscarriage, premature birth and having low birthweight babies. [16]

1.7 Types of sickle cell disease

Table 1-1 https://www.myamericannurse.com/caring-for-sickle-cell-disease/

Sickle cell disease (SCD) genotypes influence complication risks and potential disease severity.

Genotype	Hb (g/dL)	HbS (%)	HbA (%)	Typical severity
AS (sickle cell trait)	Normal	≤40	>60	Normal
SS (sickle cell anemia)	6 – 9	>90	0	Severe
Sß0 thalassemia (sickle cell anemia)	7 – 9	>80	0	Severe
Sß+ thalassemia	9 – 12	>60	10 – 30	Less severe
SC	9 – 14	50	0	Less severe

Hb = hemoglobin, HbS = hemoglobin sickle, HbA = hemoglobin A. Adapted from National Heart, Lung, and Blood Institute 2014 guidelines.

Hemoglobin is the protein in red blood cells that carries oxygen. It normally has two alpha chains and two beta chains. The four main types ofsickle cell anemia are caused by different mutations in these genes. [17]

Hemoglobin SS disease

Hemoglobin SS disease is the most common type of sickle cell disease. It occurs when you inherit copies of the hemoglobin S gene from both parents. This forms hemoglobin known as Hb SS. As the most severe formof SCD, individuals with this form also experience the worst symptoms at a higher rate.[17]

Hemoglobin SC disease

Hemoglobin SC disease is the second most common type of sickle cell disease. It occurs when you inherit the Hb C gene from one parent and theHb S gene from the other. Individuals with Hb SC have similar symptoms to individuals with Hb SS. However, the anemia is less severe. [17]

Hemoglobin SB+ (beta) thalassemia

Hemoglobin SB+ (beta) thalassemia affects beta globin gene production. The size of the red blood cell is reduced because less beta protein is made. If inherited with the Hb S gene, you will have hemoglobin S beta thalassemia. Symptoms are not as severe. [17]

Hemoglobin SB 0 (Beta-zero) thalassemia

Sickle beta-zero thalassemia is the fourth type of sickle cell disease. It alsoinvolves the beta globin gene. It has similar symptoms to Hb SS anemia.
However, sometimes the symptoms of beta zero thalassemia are more severe. It is associated with a poorer prognosis. [17]

Hemoglobin SD, hemoglobin SE, and hemoglobin SO

These types of sickle cell disease are rarer and usually don't havesevere symptoms. [17]

Sickle cell trait

People who only inherit a mutated gene (hemoglobin S) from one parentare said to have sickle cell trait. They may have no symptoms or reducedsymptoms. [17]

1.8 Sickle cell anemia diagnose

All newborns in the United States are screened for sickle cell disease. Prebirth testing looks for the sickle cell gene in your amniotic fluid.
In children and adults, one or more of the following procedures may alsobe used to diagnose sickle cell disease.

Detailed patient history

This condition often first appears as acute pain in the hands and feet.Patients may also have:

- severe pain in the bones
- anemia
- painful enlargement of the spleen
- growth problems
- respiratory infections
- ulcers of the legs
- heart problems

Blood tests

Several blood tests can be used to look for SCD:

- Blood counts can reveal an abnormal Hb level in the range of 6 to 8 grams

per deciliter.

- Blood films may show RBCs that appear as irregularly contractedcells.
- Sickle solubility tests look for the presence of Hb S.[16] Hb

Electrophoresis

Hb electrophoresis is always needed to confirm the diagnosis of sickle celldisease. It measures the different types of hemoglobin in the blood. [16]

1.9 Treatment and Management

SCD causes a range of acute and long-term complications, requiring a multi-disciplinary approach, involving various medical specialists. In the United Kingdom, comprehensive SCD care is coordinated by specialist haemoglobinopathy teams. Such teams play a key role in education about SCD for patients and their families, as well as guiding treatment with disease-modifying therapies, access to psychology, social and welfare support. Additionally, they coordinate screening services such as Transcranial Doppler (TCD) ultrasound monitoring in children, detection of iron overload or allo-antibody formation in individuals on transfusion programmes, and referral to specialists for major organ complications with an interest in SCD.[46]

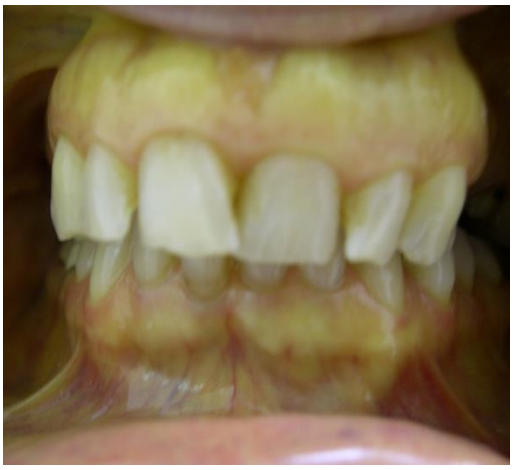
1.10 Oral Manifestations

1.10.1 Oral Mucosa and Tongue.

The most common intraoral manifestation of SCD is mucosal pallor and jaundice. This is caused by premature breakdown of RBCs in the spleen and the low number of available RBCs in the blood vessels leading to hemolytic anemia and hyperbilirubinemia [18,19]

Due to the low blood oxygen, the color of the skin turns pale. This alsocan be observed

in the intraoral buccal and labial mucosa, as well as the gingiva[18].



Picture 1.2 oral mucosa of patient with sickle cell anemia

1.10.2. Enamel and Dentin

There have been conflicting re- search results about the effect of SCD on teeth. A micro- radiography study of the dental tissues in SCD patients revealed diffused hypo mineralized zones in tooth enamel. The study also found unusual inclusions in the lumens of the dentinal tubules and pulp chambers were found to contain denticle-like calcified bodies [20]. Many studies have re- ported enamel hypoplasia, dentin hypoplasia, and delayed tooth eruption in SCD patients [21]. There has been no distinct, evidence-based research demonstrating an association between SCD and greater risk of caries. How- ever, there are several studies indicating that developmental enamel defects such as hypoplasia are postulated to have increased susceptibility to dental caries [21, 22]. Defective enamel sites (hypoplasia or hypocalcification) may provide a suitable local environment for adhesion and colonization of cariogenic bacteria, and bacteria may be retained at the base of defects in contact with exposed dentin, enabling dental caries to develop more rapidly [22, 23]. Some studies have reported that patients with SCD are less susceptible to early childhood caries. Fakuda et al. concluded that that long-term use of penicillin prophylaxis in SCD patients may prevent the acquisition of Mutans Streptococci, resulting in significantly lower caries rates in this population. This benefit occurs

only during active administration of the drug, however, and only delays the acquisition of Mutans Streptococci [25].

1.10.3 Dental Pulp

The primary reason people with SCD visit dental providers is extreme pain and sensitivity. One way to explain this pain is due to caries approaching the pulp, resulting in inflammation of the pulp, acondition known as pulpitis. Another effect of SCD on the dental pulp is Vaso occlusive crisis, when obstruction of the microcirculation in the pulp produces symptomatic and asymptomatic pulpal necrosis without any signs of odontogenic pathology in an apparently healthy tooth [26-28].

Furthermore, arbitrated blood supply may cause blood clots within the blood vessel, commonly known as blood thrombosis, which can result in calcified pulp stones in the pulp chamber [19-20]

1.10.4 Mental Nerve Neuropathy: "Numb Chin Syndrome"

Vasculo-occlusion (VOC) in the maxillofacial region can also occur in the narrow canals of major nerves supplying the maxilla and the mandible causing loss of sensation and neuropathy. Because they pass through the narrow foramina and boney canals, the mental nerve and inferior alveolar nerve are the two major nerves that are vulnerable to VOCs. This infarction of the blood supply to the nerves can cause loss of sensation andpersistent anesthesia to the lower lip and chin, which can last up to 24 months.

The first to describe mental nerve neuropathy as a result of SCD was Konotey-Ahulu in 1980. He found that 4% of patients had moderate-to- severe pain in the mandible during a sickle cell crisis, with many developing burning sensations and numbness in the lower lip along the path of the mental nerve. That recovery of sensation could take months [28]. Another case report was of a 40-year-old black man

who described that hisright mandibular first premolar, canine, and incisors “felt like wooden blocks.” A needle prick test was performed, and it was determined that the patient had profound anesthesia in the regions supplied by the mental nerve. A radiograph of the right mental nerve showed a 2 × 1 cm ovoid radiolucency, which was deciphered to be decreased trabeculation or an acute bony infarct of the mandible as a result of his sickle cell crisis.

This lesion in the mandible was similar to other lesions found in the patient’s pelvis and both right and left femoral heads. The pain eventually disappeared, although there was still numbness in the lower lip. The patient was followed for 12 months, with no changes in radiographic findings of radiolucency and loss of sensation in the lower lip[19-29].

1.10.5 Alveolar Bone and Radiographic Manifestation

Radiographic features in SCD have multiple causes. First and foremost is bone marrow hypertrophy and erythroblastic hyperplasia due to increased numbers of sickle cells and their premature destruction, causing low numbers of RBCs. Consequences of this are changes in the trabecular pattern of the bone, including loss of fine trabeculae and formation of large bone marrow spaces [18,19 ,21.] Thus, dental radio- graphs may appear to have distended medullary spaces and diminished trabeculation. There may be thinning of the cortical plate, and the inferior border of mandible may appear irregular and dissipated on the radiographic [19].

Another important feature of the SCD patient is developmental enamel hypo mineralization and hypoplasia, which can affect enamel translucency and may be seen radiographically.

Maxillary sinus opacification may be observed in patients with SCD due to bone marrow hyperplasia of the maxillary sinus [19 21 23].

There are many challenges when working with patients with SCD. We have reviewed these challenges in more detail in Table 1.

1.11 General Recommendations for Oral Health Management in Dental Practice

1.11.1 Early Intervention.

Patients with SCD are often seen in the emergency department due to severe pain. Likewise, they frequently present to dental clinics for emergency appointments rather than preventive care. Thus, by the time they come to a dental office, their oral health is quite deteriorated. Preventive dental therapy is ideal for sickle cell disease patient. The goal of the pediatric dentist is to improve and maintain excellent oral health in order to decrease the possibility of various oral infections [23]. Treatment should never be initiated during a crisis unless it is inevitable as in emergency situations.

Hence, it is important to establish routine dental visits and comprehensive care from the beginning. It is crucial that patients are educated about good oral hygiene and encouraged to have periodic oral health screening and prophy at least every 6 months [24]. Individuals with SCD should be encouraged by their medical providers to seek regular dental care.

It is critical to maintain a multidisciplinary and collaborative approach to health care management, including the primary care physician, hematologist, and dentist to ensure that the patient is receiving a well- planned com- prehensive treatment [23]. This is essential to ensure the patient is comfortable with their healthcare team so their condition can be managed before it worsens into sickle cell crisis. Education and spreading awareness of the importance of daily oral health care, as well as encouragement of patients to maintain regular dental check-ups and dental cleanings, is essential. Thus, conducting oral health promotions and screening programs for individuals with SCD is of utmost importance [23].

1.11.2 Strategies to Manage Dental Anxiety.

The physical, emotional, and social disabilities from life-long medical and dental issues reinforces dental anxiety over painful proce- dures, such as tooth extractions, and contributes to avoid- ance of dental visits [35, 38] Dental anxiety can be multifactorial and proper evaluation is crucial to identify root causes [35, 37] Recognizing the etiology and severity of anxiety can help the dental provider better formulate a plan to ensure increased compliance with recommendations.

Evaluation of anxiety can be performed during the initial appointment. Providers can ask patients about their feelings regarding procedures, anesthesia, and sounds along with past dental experience. This can help to inform providers of the patient's level of anxiety prior to dental procedures, so measures can betaken to alleviate their anxiety and make the visit as comfortable as possible [33] [38].

It is important to communicate with the patient regarding the optimal time for their appointment. In general, short morning appointments are recommended.

Pharmacological pain management methods are advised for the mildly anxious patient, which can be achieved by the use of anxiolytics and sedatives, such as midazolam or diazepam [24, 25]. Use of nitrous oxide gas, alone or in combination with a sedative, is also found to be an effective approach for management of dental anxiety in mild-to-moderate cases [39]

In the case of the highly anxious patient requiring ex- tensive multiple dental or surgical procedures, general an- esthesia is the most recommended approach [33].

Nonpharmacological pain management strategies include the use of relaxation strategies such as imagery, deep breathing, and distraction. Inaddition, finding ways to improve the comfort of the environment (e.g., playing music) is another way to help patients feel more relaxed and thus reduce their pain [39].

1.11.3 Restorative Management.

Many factors contribute to caries prevalence in SCD, including salivary buffering capacity, salivary flow, improper oral hygiene, systemic conditions, socioeconomic status, and medications [40]. It is important that more proactive measures and a strategicapproach are taken to prevent caries and disease spread.

A) Caries diagnosis: early detection of caries is the key to prevention. Thus, regular visits to a dentist, at least every 6 months, are recommended for early detection and prevention of dental caries [41].

B) Oral hygiene: patient and community education to increase awareness of appropriate oral care is of utmost importance. This includes an emphasison removing dental plaque daily by brushing twice a day, daily flossing, and use of oral rinses. It is important that the correct brushing techniques are explained and demonstrated for the most effective and efficient results [42]

C) Protective methods: regular use of fluoride containing products such as toothpaste, oral mouth- wash, fluoride varnish, and calcium phosphate agents can help prevent caries and reverse the oral microflora environment. Pit and fissure sealants, antibacterial, and antimicrobial are other important protective agents [33].

D) Diet consultation: high sugar dietary content is a common and well- known etiology of dental caries. Informing patients about the relationship between diet and oral health and helping them reduce sugar content is a helpful way to prevent dental caries [42]. Use of sugar substitute products such as xylitol, which has anticariogenic properties, should be introduced. Consultation with a dietician can help patients understand their individual nutritional needs to determine the appropriate amount and frequency of sugar intake [35]. In addition to the amount of sugar intake, the frequency with which teeth are exposed to sugary substances contributes to poor oral health and reducing such frequency is crucial in preventing dental caries.

E) Proactive dental caries treatment: in addition to early diagnosis of dental caries, early intervention is imperative to maintain good oral health. Dental caries can progress aggressively; thus, direct and indirect restorative procedures should be completed in a timely manner to prevent further deterioration of the dentition [42].

1.11.4 Dental Implants.

Dental implants are a widely acceptable procedure to replace single or multiple missing teeth. Dental implants are not contraindicated in sickle cell patients; however, it is very crucial to understand this dis- order and its clinical physiology to avoid any complications. Due to various clinical manifestations of sickle cell disease, such as osteonecrosis of bone where the blood supply to the jaw is compromised due to clotting in the blood vessels, can cause failure of dental implants [45]. Nevertheless, with meticulous understanding of the nature of the disease, se- verity of the condition and previous response to procedures can help to plan successful surgery with minimal postop- ergative complications [46].

Additionally, complete blood count (CBC) and radiographs should be done as a part of the treatment plan. Depending on the CBC results, the patient may need a blood transfusion before or after the surgery to reduce the sickle cell concentration in the blood. In the case where patient may need a blood transfusion, implant surgery should be carried out in the hospital- based setting, with collaborative participation of hematologist and primary care physician [38]. The application of the immediate installation technique has the advantage of achieving satisfactory results with a high success rate.The use of this technique reduces the number of surgical interventions and shortens the time between tooth extraction and permanent installation of the prosthesis, eventually avoiding the process of bone re- sorption, thereby leading to the preservation of alveolar ridge in terms of proportion,size, and width [47].

1.11.5 Orthodontic Management

Apart from the other orodental manifestations, certain cephalometric changes are characteristic in SCD patients [48]. Orthodontic treatments for the sickle cell disease patient are strictly elective as these patients may have malocclusions or skeletal abnormalities, so their correction can improvise the child's self-esteem. Some of the common malocclusion features in SCD, including incisal crowding, overjet, open bite, and posterior open bite, are distinctive. Additionally, inclination towards a class II molar relationship, delayed tooth eruption, and increased crowding in the lower anterior region is prominent in children with SCD. It is highly suggested that patients with SCD get orthodontic treatment at the earliest appropriate opportunity to avert problems associated with malocclusions and avoid other complications later in life. Timely orthodontic treatment can help improve quality of life. Orthodontic treatment basically moves teeth through remodeled bone or changes growth patterns by repositioning the lower jaw.

However, the disease process of sickle cell disease may compromise the outcome of the planned treatment (van Venrooy and Proffit, 1985) and therefore, treatment ought to be monitored closely, especially during a crisis. Also, orthodontic appliances should be designed with great cautionto prevent irritation of soft tissues.

1.11.6 Infection Management

Patients with SCD are at higher risk than the general population of infection, in- clouding dental infection [24]. There are several factors contributing to this. Contributing risk factors for various dental and periodontal infections include daily smoking, older age, and lack of daily dental flossing. One of the best ways to prevent dental infection is the early detection and elimination of periodontal and dental sources of infection. Dental infection can impact systematic health through various pathways,

Dental infection may also trigger or aggravate sickle cell crises. Thus, all oral infections must be treated aggressively at the local and systematic levels. They must be treated with suitable antimicrobial agents such as antibiotics and rinses. In the case of the severe infection, hospitalization is recommended for administration of intravenous antibiotics, fluids, pain control, and monitoring. Prophylactic antibiotic is recommended for invasive and extensive surgical procedures to prevent systemic infections, Vaso occlusive crisis, and osteomyelitis [22].

However, during sickle cell crisis only acute infections or trauma should be treated, delaying elective procedures until the crisis is resolved.

Conclusion

Sickle cell disease (SCD) is a group of blood disorders typically inherited from a person's parents. The highest frequency of sickle cell disease is found in tropical regions, particularly sub-Saharan Africa, tribal regions of India, and the Middle East. The loss of red blood cell elasticity is central to the pathophysiology of sickle cell disease. Sickle cell anemia is caused by a mutation (change) in one of the genes for hemoglobin (the substance inside red blood cells that binds to oxygen and carries it from the lungs to the tissues). Sickle cell anemia is a monogenic disease but presents a very complex phenotype and very variable clinical manifestations between subjects. Sickle cell anemia is caused by a change in the gene that tells the body to make the iron-rich compound in red blood cells called hemoglobin.

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