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Publications 2023

OPEN ACCESS
ONLINE ISSN: 2992-5797
PRINT ISSN: 2992-6122

NEWPORT INTERNATIONAL JOURNAL OF BIOLOGICAL AND APPLIED SCIENCES (NIJBAS)

Volume 4 Issue 1 2023

https://doi.org/10.59298/NIJBAS/2023/1.1.11111

Current Advances in the Diagnosis and Treatment of Sickle Cell Anaemia

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ABSTRACT

Sickle cell anemia (SCA) presents a complex challenge globally due to its significant morbidity and mortality. Recent advancements in diagnostic tools and treatment modalities have revolutionized the management of this hereditary hemoglobin disorder. This paper aims to synthesize current breakthroughs in the diagnosis and treatment of sickle cell anemia. Diagnostic techniques including genetic testing, hemoglobin electrophoresis, and advanced imaging methodologies are explored, providing insights into their accuracy and clinical applicability. Moreover, novel therapeutic approaches such as gene editing, fetal hemoglobin induction, and targeted therapies are discussed for their potential in ameliorating SCA-related complications and improving patient outcomes. The paper also assesses the challenges and future prospects in the field, emphasizing the need for comprehensive strategies that encompass early detection, personalized interventions, and ongoing research efforts. Understanding these recent strides in both diagnostics and therapeutics is pivotal in enhancing the care and prognosis of individuals afflicted with sickle cell anemia.

Keywords: sickle cell anaemia, anaemia, treatment, diagnosis

INTRODUCTION

Sickle cell disease (SCD) is an inherited single-gene autosomal recessive disorder caused by the 'sickle' gene, which affects haemoglobin structure, and it originates from a single β-chain substitution of glutamic acid by valine [1-3]. This stems from an A-for-T substitution at codon 6 of the β-globin gene that causes haemoglobin polymerisation in the red blood cells during hypoxia [4-6]. It is inherited in an autosomal recessive pattern, either in the homozygous (Hb SS) state or compound heterozygous state (in which Hb S is inherited in combination with another haemoglobin variant, like Hb SC, Hb SD, Hb SB-thalassaemia) [7-9]. Clinical manifestations of SCD vary from mild, almost asymptomatic, to severe forms associated with high mortality rates [10]. Clinical manifestations usually appear after six months of age, when fetal haemoglobin (Hb F) concentration decreases [11]. Due to repeated vaso-

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ONLINE ISSN: 2992-5797
PRINT ISSN: 2992-6122

occlusive crises, it may result in multi-organ failure [12]. SCD is associated with premature mortality with a median age of death of 43 years (IQR 31.5–55 years) [13-14]. Treatment requires early diagnosis, prevention of complications and management of end-organ damage. Within the umbrella of SCD, many subgroups exist, namely sickle cell anemia (SCA), hemoglobin SC disease (HbSC), and hemoglobin sickle-beta-thalassemia (beta-thalassemia positive or beta-thalassemia negative). Several other minor variants within the group of SCDs also, albeit not as common as the varieties mentioned above. Lastly, it is essential to mention the sickle cell trait (HbAS), which carries a heterozygous mutation and seldom presents clinical signs or symptoms [15-17].

There are two states of sickle cell anaemia (SCA), the steady state refers to a point in time where the patient is otherwise stable and not experiencing an acute painful crisis or having an infection or other acute complications of the disease. The other state is termed "crisis", this refers to the periodic episodes of pain developed when sickle-shaped red blood cells block blood flow through tiny blood vessels to the chest, abdomen, joints, and bones [18].

Recent advances in the field, more so within the last three decades, have alleviated symptoms for countless patients, especially in high-income countries. In 1984, Platt et al. first reported the use of hydroxyurea in increasing the levels of HbF. Since then, the treatment of sickle cell has taken to new heights by introducing several new agents (voxelotor, crinzalizumab, L-glutamine) and, most recently, gene therapy [19].

EPIDEMIOLOGY OF SICKLE CELL ANAEMIA

In Nigeria, the prevalence of SCD is 20-30/1000 live births [20]. Sadly, SCD alone contributes to 9-16% of under-five mortality in many West African countries [21]. About 5–7% of the global population carries an abnormal haemoglobin gene. The most predominant form of haemoglobinopathy worldwide is sickle cell disease. The greatest burden of the disease lies in sub-Saharan Africa and Asia [22]. The high prevalence of SCD in sub-Saharan Africa has been attributed to the survival advantage conferred by the sickle cell trait against *Plasmodium falciparum*. The relative protection of individuals with sickle cell trait to severe *Plasmodium falciparum* infestation creates a selective pressure that has maintained the sickle cell gene within human populations in malaria-endemic regions like sub-Saharan Africa. A phenomenon referred to as balanced polymorphism [23-24].

PATHOPHYSIOLOGY OF SICKLE CELL ANAEMIA

The pathophysiology of SCD is a consequence of polymerisation of abnormal haemoglobin under low-oxygen conditions, which leads to the formation of rigid and fragile sickle-shaped red cells. These sickled cells are prone to increased haemolysis, which causes anaemia; they are also responsible for vaso-occlusion in the small blood vessels. Haemolysis and vaso-occlusion are implicated in most of the clinical features and complications of SCD [25].

Sickle cell disease is a qualitative haemoglobinopathy resulting from a structural change in the sequence of amino acids on the beta globin chain of the haemoglobin molecule due to a point mutation. This mutation causes a single base change from adenine to thymine on the 17th nucleotide of the beta-globin chain gene. This invariably translates into the substitution of valine for glutamic acid at position 6th of the amino acid of the beta-globin chain [26-27]. The abnormal biochemistry of this mutant haemoglobin induces polymerisation of Hb S molecules within the red cells; the initial step in sickling. On the sickled haemoglobin, the glutamic acid molecule, which is hydrophilic, polar, and negatively charged, is replaced by a less polar, hydrophobic, neutral amino acid, valine. Under deoxy conditions, the abnormal valine residue causes intra-erythrocytic hydrophobic interaction of sickle haemoglobin tetramers, leading to their precipitation and polymer formation, otherwise called gelation [28]. Eventually, all cytosolic haemoglobin molecules precipitate into seven (one inner and six outer) double strands with cross-links which are called tactoids. Upon reoxygenation, unsickling occurs and the red cell reassumes its normal shape. However, repeated sickling and unsickling of the red cell damage the red cell membrane, due to herniation of sickle haemoglobin polymers through the cytoskeleton, thus rendering the red cell permanently sickled. These appear as irreversibly sickled cells (ISCs) on peripheral blood cytology [29-30].

COMPLICATIONS

Acute complications of SCD include ischemic, vasoocclusive (pain) crises, acute chest syndrome, stroke, splenic sequestration, acute renal failure, and cholecystitis.

Chronic complications include chronic pain, cholelithiasis, renal dysfunction, hypertension, pulmonary hypertension, retinopathy, leg ulcers, avascular necrosis of the head of femur and humerus as well as increased propensity for infections and sepsis [31].

LABORATORY DIAGNOSIS

A. Conventional Diagnostic method

1. Screening tests
    - Sickling test: Sickling tests are mainly based on the polymerisation of Hb S in the deoxygenated state. The solubility test is the most widely used nowadays; its principle is based on the insolubility

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PRINT ISSN: 2992-6122

of Hb-S in the presence of concentrated phosphate buffer, a haemolyzing agent, and sodium dithionate. These agents crystalize the Hb S and precipitate the cells, which refract the light and cause solution turbidity. The result is compared with negative and positive controls [32].

- Solubility test: It is a technique that depends on the filtration properties of the paper substrate and on the insolubility of the Hb S, where it can be visually interpreted to detect the presence of hemoglobin S. In this test, one drop of the blood sample is mixed with a hemoglobin solubility agent with a ratio of 1:10. Then, the mixture is placed onto chromatography paper followed by staining. A different stained blood pattern forms based on the hemoglobin, these stains are used to determine Hb SS, the carrier Hb AS, and normal hemoglobin Hb AA. The test shows 94.2% sensitivity and 97.7% specificity for the visual detection of the Hb S. In Hb SS it gives reddish residue and a clear filtrate [32].

2. Full Blood Count (FBC): The full blood count (FBC) is a primary test to characterize the different types of anemia. However, the hemoglobin mutation will affect the hematological parameters, showing a variable change. Patients with sickle cell anaemia usually present with the following result
    - Anaemia
    - Neutrophilia
    - Thrombocytosis
    - Elevated Mean corpuscular volume (MCV)
    - Elevated Red cell distribution width (RDW) [33].
3. Peripheral Blood film: The peripheral blood smear (PBF) is usually done after spotting abnormality in the automation counts and is considered a landmark of any hematological evaluation. PBF examines the morphology of the blood cell and evaluates any microscopic changes, which can provide valuable information that helps in the diagnoses of the different types of anemia. The blood film analysis is too complicated due to the changes in the cell's edge, location, shape, and size. As a result, a computerized system has been developed to provide a more accessible way to recognize the type of anemia. In sickle cell anemia the following features are seen
    - Normocytic normochromic
    - Irreversible Sickle Cells (ISCs)
    - Nucleated Red Blood Cells (NRBCs)
    - Target cells
    - Neutrophilia
    - Thrombocytosis [33].
4. Haemoglobin electrophoresis –Electrophoresis is a type of chromatography techniques, and it is considered as one of the important tests used to detect Hb variants [34]. In this test, an electrical field is applied to facilitate the migration of electrically charged molecules. The first described hemoglobin variant Hb-S by using electrophoresis was in 1949. To identify hemoglobin variants, different pH and mediums are used, either cellulose acetate electrophoreses at alkaline pH or citrate agar at acidic pH [35].

B. Advanced diagnostic method

1. Prenatal testing
    - Amniocentesis: Aminocentesis is a test that is offered during pregnancy to check if the baby has a genetic or chromosomal condition, such as, sickle cell disease, thalessaemia, down syndrome etc**.** Amniocentesis is usually carried out between the 15th and 20th weeks of pregnancy, but it can be done later if necessary. It can be performed earlier, but this may increase the risk of complications of ammiocentesis and is usually avoided. During the test, a long, thin needle is inserted through your abdominal wall, guided by an ultrasound image. The needle is passed into the amniotic sac that surrounds your baby and a small sample of amniotic fluid is removed for analysis. The test itself usually takes about 10 minutes, although the whole consultation may take about 30 minutes. The test result will show whether the baby have a genetic condition of sickle cell anemia [36].
    - Chorionic Villus Sampling: CVS can be safely done early in pregnancy from about 9½ weeks after your last menstrual period. The best timing is between 10 and 14 weeks. A small amount of material is taken from the developing placenta which develops from the tissues of the baby, not of the mother, so it has the same genes as the baby. It is made of up of chorionic villi. Villi is plural for villus. Two routes may be taken to obtain a sample of chorionic villi; either through the

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PRINT ISSN: 2992-6122

abdomen (tummy) or through the cervix of the uterus via the vagina. Most samples are therefore obtained through the abdomen and this route leads to a much lower chance of a miscarriage of the pregnancy than going through the vagina and cervix. An ultra sound scan is used so that we can see what we are doing. A local anaesthetic is injected into the skin in order to prevent pain before the insertion of the needle the obstetrician fixes a syringe through the abdomen and into the womb and gently removes some chorionic villi. Alternately, the obstetrician puts very thin forceps through the vagina and then into the womb. It is so thin that most women hardly feel it. It does not touch the baby, or the little bag of water surrounding the baby. Then the forceps are opened and closed to take a very small sample of chorionic villi from the placenta. Once the sample has been obtained, its immediately examined under a microscope to check that it is the right sample from the placenta. If it is, we stop. If it is not the correct sample, we manipulate the tip of the tube or needle slightly to obtain the right sample. The test usually takes 10 to 20 minutes. DNA from the chorionic villi is studied to see if the baby's genes for haemoglobin are normal, or if an alteration has been passed on from the parents [36].

2. High Performance Liquid Chromatography (HPLC): HPLC is documented to separate the haemoglobin fractions as they have different interaction with the stationary phase. HPLC detects different types of haemoglobin based on the retention time and shape of the peak [37]. Each haemoglobin has a specific retention time and can be compared with the retention time of the known haemoglobin fractions [34] HPLC is used to detect and quantify HbF, Hb A2, HbS, HbC, Hb Barts, and other Hb variants [34]. Developing a fully automated HPLC would be useful in testing a large number of samples accurately. HPLC shows better sensitivity in separation of hemoglobin variants than electrophoresis. HPLC is much less labor-intensive and more reliable for monitoring patients under blood transfusion or hydroxyurea [38]. However, HPLC is an expensive machine and cannot differentiate among all variants with the same retention time. For example, all Hb variants with a similar retention time to are eluted out with the Hb S peak. Therefore, it can misdiagnose new variants that mimic Hb S. Thus, HPLC cannot stand alone as a diagnostic test and should be done along with a confirmatory test such as DNA analysis before giving a final diagnosis [39].

3. Genetic analyses: The genetic study is important for the precise detection of the various types of sickle cell disease, based on the detection of β-globin mutations that lead to sickle cell disease development [40].
    a. Polymerase Chain Reaction (PCR)-Based Techniques. Polymerase chain reaction is one of the most powerful diagnostic techniques, where special enzymes are used to amplify specific parts of the genetic materials to millions of copies, using specific primers. PCR can detect well known single genes or several genes in a single tube. The PCR program involves denaturation, annealing, and elongation, which is repeated for 20–40 thermal cycles. Then, the result can be detected by gel electrophoresis, sequencing, melting curve analysis, or monitoring the change in the fluorescence. PCR sensitivity and specificity have revolutionized the prenatal and neonatal diagnostic field. Several PCR-based techniques are documented to detect βs mutations, such as high-resolution melting (HRM) analysis, which is simple, sensitive, and cost-effective for use in mass screening of SCD genotypes [41]. .Another simple, low-cost PCR-based technique has been developed using bi-directional allele-specific amplification (ASA) and a hot star system to provide more specific single-tube genotyping, where the point mutation of sickle cell anemia is used as the SNP model. In addition, discriminatory conditions have enabled the determination of homozygous and heterozygous states based on the different band sizes on the agarose gel electrophoresis [42].
    b. Restriction Fragment Length Polymorphism: Restriction fragment length polymorphism (RFLP) is used to detect sickle cell disease based on restriction enzymes, which remove the recognition site at the βs mutated gene. For example, MstII is one of the first described restriction enzymes; it cuts the DNA in the sequence CCTNAGG (where N represents any nucleotide). Therefore, when thymine replaces the adenine, it removes the recognition site for MstII restrictase. After separation, the number of bands resulting from the enzyme cutting indicates the number of mutations. In a healthy individual with (βA βA), the gene is cut by the MstII restrictase and yields two bands. In homozygotes, the restrictase cuts both genes,

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PRINT ISSN: 2992-6122

and two short bands appear. In the sickle cell trait (βAβS), no cut is made in the βS, so a single band appears; however, the βA gene is cleaved, and two bands appear. In sickle cell anemia homozygous (βSβS), there is no enzyme cutting due to the mutation in both genes, so a single wide band appears. Another restriction enzyme has been used in sickle cell detection is Ddel I. The mutation caused sickle cells anaemia (SCA) removes the restriction site of Ddel I, 5′-GTNAG-3′. As a result, bands with different lengths appear depending on the presence of sickle cell anemia mutation [43].

4. Lateral Flow Immunoassay: Lateral flow assays (LFAs) are widely used as portable platforms in biomedical detection. Kanter et al. demonstrated a sensing platform called Sickle SCAN. It is used to detect normal haemoglobin Hb AA, sickle cell trait Hb AS, haemoglobin C trait Hb AC, sickle-haemoglobin C disease Hb SC, and haemoglobin C disease Hb CC. The test used polyclonal antibodies on lateral flow chromatographic immunoassay against haemoglobin S, haemoglobin C, and haemoglobin A to detect the different types of SCD qualitatively. The polyclonal antibodies are attached on the test strip; the sample migrates in the absorbent pads, where the antibody conjugated to the nanoparticles binds to the hemoglobin; and then both migrate to the test strip. The haemoglobin binds with the corresponding antibody and produces blue line. The Sickle SCAN cartridge contains four detection bands: the control band, normal Hb A, Hb S band, and Hb C band. The test can be performed within minutes and costs a few dollars per test [44]. Mcgann *et al.* tested the validation of the Sickle SCAN assay to detect different haemoglobin. The test was performed using 139 whole blood samples (venous samples, dried blood spots, and spiked blood samples), and the results were compared to capillary electrophoresis (CZE) [45]. The test's accumulative sensitivity and specificity for Hb SS were 98.4% and 98.6%, respectively. The cumulative sensitivity and specificity for the diagnosis of Hb SC disease were 100%. A neonate sample with a high amount of Hb F was tested and demonstrated that the detection of Hb S or Hb C was not affected by the high concentration of HbF. Furthermore, they examined the test's storage condition and documented that the device can be stored at 37 °C for 30 days. However, the test suffers from some limitations such as misinterpretation of the result due to visual reading, cross-reactivity of the polyclonal antibody, and false-positive results in detecting the Hb A heterozygous with Hb S. The authors recommended another validation for the sickle SCAN in primary healthcare centers [45].

MANAGEMENT/ TREATMENT

1. PAIN MANAGEMENT

- Vasoocclusive crisis is treated with vigorous hydration and analgesics
  - ✓ Normal saline and 5% dextrose in saline may be used
  - ✓ These fluids should be given intravenously, and treatment must be in an inpatient setting
  - ✓ Intravenous fluids should be of sufficient quantity to correct dehydration and to replace continuing loss, both insensible and due to fever
- Chronic pain is managed with long-acting oral morphine preparations and acetaminophen and non-steroidal anti-inflammatory drugs (NSAIDs)
  - ✓ NSAIDs are particularly effective in reducing deep bone pain. Many patients may require breakthrough oral opiates as well. The weak agents, codeine and hydrocodone, are used first. Sustained-release long-acting oral morphine is reserved for more severe cases.
  - ✓ The addition of tricyclic antidepressants may reduce the dose and need for opiates by interfering with pain perception. Many patients with chronic pain are depressed, and lifting the depression has a salutary effect on the pain [46].
- Non pharmacological approaches to pain management are very important.
  - ✓ These include physical therapy, heat and cold application, acupuncture and acupressure, hypnosis, and transcutaneous electric nerve stimulation (TENS).
  - ✓ All of these modalities may have a substantial impact on pain reduction (Ballas, 2007}.

2. BLOOD TRANSFUSIONS

These are used to treat and prevent complications, such as stroke, in people with sickle cell disease.

In a red blood cell transfusion, red blood cells are removed from a supply of donated blood, then given through a vein to a person with sickle cell anemia. This increases the number of normal red blood cells, which helps reduce symptoms and complications. Healthcare providers also recommend blood transfusions

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for children who have abnormal transcranial Doppler (TCD) ultrasound results, because transfusions can lower the chance of having a first stroke. blood transfusion can also be used to treat complications that do not improve with hydroxyurea. Providers may also use transfusions in people who have too many side effects from hydroxyurea [47]. Risks include an immune response to the donor blood, which can make it hard to find future donors; infection; and excess iron buildup in your body. Because excess iron can damage your heart, liver and other organs, you might need treatment to reduce iron levels if you undergo regular transfusions [47].

DRUGS THERAPHY

The FDA approved hydroxyurea in 1998 for adults with SCD. Subsequently, hydroxyurea was FDA approved for children in 2017 to reduce the frequency pain events and need for blood transfusion in children less than 2 years [48]. However, there is an improve in the treatment with the recent FDA approval of 3 other treatments – L-glutamine and crizanlizumab for reducing acute complications and voxelotor for improving anaemia [48-51]. Other therapies in current development focus on inducing fetal haemoglobin, reducing anti-sickling or cellular adhesion or activating pyruvate kinase – R [46].

- L-glutamine
  Glutamine I required for the synthesis of glutathione, nicotinamide adenine dinucleotide and arginine. The essential amino acid protects red blood cells against oxidative damage, which forms the basis for it is proposed utility in SCA. It helps in reducing the frequency of pain crises. The exact mechanism in SCA, however, is not clear [50]. Common side effect includes GI upset (constipation, nausea, abdominal ache and headaches).
- Crizanlizumab
  P-seclectin expression, triggered by inflammation, promotes adhesion of neutrophils, activated platelets and sickle red cells to the endothelial surface and to each other, which promotes vaso-occlusion in SCA. Crizanlizumab, given as a monthly intra-venous infusion, is a humanized monoclonal antibody that binds P-selectin and blocks the adhesion molecule's interaction with its ligand, P-selectin glycoprotein ligand 1. This drug, given by injection, can help reduce the frequency of pain crises in adults and children older than 16. Adverse effects were uncommon but include headache, back pain, nausea, arthralgia and pain in the extremity [49].
- Voxelotor
  Polymerisation of Hb S in the deoxygenated state represents the initial step in red blood cell sickling, which leads to reduced red blood cell deformability and increased haemolysis. Voxelotor is a first-in-class allosteric modifier of Hb S that increases oxygen affinity. This drug is used to treat sickle cell disease in adults and children older than 12. Taken orally, this drug can lower the risk of anemia and improve blood flow throughout the body. Adverse effects include headache, GI symptoms, arthralgia, fatigue and rash (Vichinsky *et al*., 2019).

3. **STEM CELL TRANSPLANT**

Currently, bone marrow transplant also known as stem cell transplant is the only cure for SCA and this is not for everyone. Many patients who have SCD either are too old for a transplant or they don't have a donor who is Human leucocyte antigen (HLA) matched, this procedure involves replacing bone marrow affected by sickle cell anemia with healthy bone marrow from a donor. The procedure usually uses a matched donor, such as a sibling, who doesn't have sickle cell anemia.

Complications can include serious infections, seizures, and other clinical problems. About 5% of people who have received such transplants have died. Sometimes transplanted cells attack the recipient's organs. This is called graft-versus-host disease [52].

4. **GENE THERAPY**:

Genetic therapy involves either restoring a faulty or missing gene or adding a new gene that improves the way the cell works. Researchers take blood or bone marrow from a patient and modify their stem cells in a laboratory using genetic therapies.

Gene therapy may treat SCA (with or without a well-matched donor) by editing DNA in haemoglobin genes to stop the disease. It can be done by either fixing the faulty gene haemoglobin or turning on a different healthy haemoglobin gene.

MANAGEMENT OF STEADY STATE

- Folic acid supplementation
- Prevention of infection improves chances of survival in SCA.

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- Penicillin prophylaxis, commencing in infancy and continued until age 5 years or early teens
- The use of a pneumococcal vaccine at age 2 years with a booster dose at age 5 years greatly reduces the frequency of infections with S pneumoniae
- In the adult patient, all infections must be treated promptly with broad-spectrum antibiotics until a causative organism is identified and therapy is tailored according to its antibiotic sensitivity
- Malarial prophylaxis [52-63].

MANAGEMENT OF COMPLICATIONS

- Generally involves;
- ✓ specialist care and co management
- ✓ Special tests; TCD, ECHO, serum ferritin and iron monitoring
- ✓ Exchange blood transfusion
- ✓ Use of hydroxyurea
- ✓ Use of erythropoietin
- ✓ Dialysis

PREVENTION

- Early diagnosis and treatment; prevents complications
- Prompt treatment of acute presentations; prevents complications
- Rehabilitation of those who have developed life changing events
- Premarital screening, targeted at secondary school students
- Prenatal diagnosis [53-63]

FUTURE PERSPECTIVES

Gene editing is a new therapy focus whereby researchers attempt to increase the Hb F level in patients with SCA. This technique is being developed alongside HSCT. Many approaches to gene editing are in clinical trials right now.

Viral gene addition using lentivirus: The technique aims to add a modified beta or gamma-globin gene to reduce the Hb S component and increase the Hb A (beta-globin gene) or the Hb F (gamma-globin gene) [54].

CRISPR (Clustered regularly interspaced short palindromic repeats): Targets the expression of BCL11A, which normally downregulates gamma-globin expression. By introducing insertions and deletions in the BCL11A erythroid lineage-specific enhancer on chromosome 2, BCL11A is downregulated, resulting in increased expression of the gamma-globin gene, which subsequently increases Hb F [55].

CONCLUSION

A significant tool for enhancing the lives of those affected by this inherited blood illness is being educated about the most recent developments in the diagnosis and treatment of sickle cell anemia. Informed decisions, access to cutting-edge treatments, and advocacy for better care are all made possible by it for patients, their families, and healthcare professionals. For those with sickle cell anemia, there is sincere optimism for an even better future thanks to continuing research and exciting advancements in the works. We can jointly contribute to a future where people with this illness not only manage their health effectively, but also thrive with newfound vitality and resilience by staying involved and proactive.

REFERENCES

1. Obeagu, E. I., Ochei, K. C., Nwachukwu, B. N., & Nchuma, B. O. (2015). Sickle cell anaemia: a review. *Scholars Journal of Applied Medical Sciences*, *3*(6B), 2244-2252.
2. Obeagu, E. I. (2020). Erythropoeitin in Sickle Cell Anaemia: A Review. *International Journal of Research Studies in Medical and Health Sciences*, *5*(2), 22-8.
3. Obeagu, E. I. (2018). Sickle Cell Anaemia: Haemolysis and Anemia. *Int. J. Curr. Res. Chem. Pharm. Sci*, *5*(10), 20-1.
4. Rees, D., Williams, T. and Gladwin, M. Sickle-Cell Disease. Lancet [Internet]. 2010; 376 (9757): 2018–31. In.
5. Obeagu, E. I., Muhimbura, E., Kagenderezo, B. P., Uwakwe, O. S., Nakyeyune, S., & Obeagu, G. U. (2022). An Update on Interferon Gamma and C Reactive Proteins in Sickle Cell Anaemia Crisis. *J Biomed Sci*, *11*(10), 84.

OPEN ACCESS
ONLINE ISSN: 2992-5797
PRINT ISSN: 2992-6122

6. Obeagu, E. I., Bunu, U. O., Obeagu, G. U., & Habimana, J. B. (2023). Antioxidants in the Management of Sickle Cell Anaemia: An Area to Be Exploited for the Wellbeing of the Patients. *International Research in Medical and Health Sciences*, *6*(4), 12-17.
7. Modell, B. and Darlison, M. J. B. o. t. W. H. O. (2008). Global Epidemiology of Haemoglobin Disorders and Derived Service Indicators. **86(6):** 480-487.
8. Obeagu, E. I. (2018). An update on micro RNA in sickle cell disease. *Int J Adv Res Biol Sci*, *5*, 157-8.
9. Obeagu EI, Ogunnaya FU, Obeagu GU, Ndidi AC. SICKLE CELL ANAEMIA: A GESTATIONAL ENIGMA. migration. 2023;17:18.
10. Serjeant, G. R. J. C. S. H. p. i. m. (2013). The Natural History of Sickle Cell Disease. **3(10):**
11. Di Nuzzo, D. V. and Fonseca, S. F. J. J. d. P. (2004). Anemia Falciforme E Infecções. **80:** 347-354.
12. Costa, F. F. and Fertrin, K. Y. J. S. c. a. F. b. s. t. c. p. (2016). Clinical Manifestations and Treatment of Adult Sickle Cell Disease. 285-318.
13. Obeagu, E. I., & Getrude, U. Obeagu.,(2023). Evaluation of Hematological Parameters of Sickle Cell Anemia Patients with Osteomyelitis in A Tertiary Hospital in Enugu, Nigeria. *Journal of Clinical and Laboratory Research*, *6*(1), 2768-0487.
14. Obeagu, E. I., Dahir, F. S., Francisca, U., Vandu, C., & Obeagu, G. U. (2023). Hyperthyroidism in sickle cell anaemia. *Int. J. Adv. Res. Biol. Sci*, *10*(3), 81-89.
15. Njar, V. E., Ogunnaya, F. U., & Obeagu, E. I. Knowledge And Prevalence Of The Sickle Cell Trait Among Undergraduate Students Of The University Of Calabar. *Prevalence*, *5*(100), 0-05.
16. Swem, C. A., Ukaejiofo, E. O., Obeagu, E. I., & Eluke, B. (2018). Expression of micro RNA 144 in sickle cell disease. *Int. J. Curr. Res. Med. Sci*, *4*(3), 26-32.
17. Obeagu, E. I. (2023). Depression in Sickle Cell Anemia: An Overlooked Battle. *Int. J. Curr. Res. Chem. Pharm. Sci*, *10*(10), 41-44.
18. Obeagu, E. I. (2018). Sickle cell anaemia: Historical perspective, Pathophysiology and Clinical manifestations. *Int. J. Curr. Res. Chem. Pharm. Sci*, *5*(11), 13-5.
19. Obeagu, E. I., & Obeagu, G. U. (2023). Sickle Cell Anaemia in Pregnancy: A Review. *International Research in Medical and Health Sciences*, *6*(2), 10-13.
20. Adegoke, S., Adeodu, O. and Adekile, A. J. N. j. o. c. p. (2015). Sickle Cell Disease Clinical Phenotypes in Children from South. Western, Nigeria. **18(1):** 95-101.
21. Makani, J., Williams, T., Marsh, K. J. A. o. T. M. and Parasitology. (2007). Sickle Cell Disease in Africa: Burden and Research Priorities. **101(1):** 3-14.
22. Piel, F. B., Patil, A. P., Howes, R. E., Nyangiri, O. A., Gething, P. W., Dewi, M., Temperley, W. H., Williams, T. N., Weatherall, D. J. and Hay, S. I. J. T. L. (2013). Global Epidemiology of Sickle Haemoglobin in Neonates: A Contemporary Geostatistical Model-Based Map and Population Estimates. **381(9861):** 142-151.
23. Edward, U., Osuorji, V. C., Nnodim, J., & Obeagu, E. I. (2022). Evaluationof Trace Elements in Sickle Cell Anaemia Patients Attending Imo State Specialist Hospital, Owerri. *Madonna University journal of Medicine and Health Sciences ISSN: 2814-3035*, *2*(1), 218-234.
24. Obeagu, E. I. (2018). Vaso-occlusion and adhesion molecules in sickle cells disease. *Int J Curr Res Med Sci*, *4*(11), 33-5.
25. Telfer, P., Coen, P., Chakravorty, S., Wilkey, O., Evans, J., Newell, H., Smalling, B., Amos, R., Stephens, A. and Rogers, D. J. h. (2007). Clinical Outcomes in Children with Sickle Cell Disease Living in England: A Neonatal Cohort in East London. **92(7):** 905-912.
26. Ifeanyi, O. E., Stella, E. I., & Favour, A. A. (2018). Antioxidants In The Management of Sickle Cell Anaemia. *Int J Hematol Blood Disord (Internet) 2018 (cited 2021 Mar 4); 3. Available from: https://symbiosisonlinepublishing. com/hematology/hema tology25. php.*
27. Nnodim, J., Uche, U., Ifeoma, U., Chidozie, N., Ifeanyi, O., & Oluchi, A. A. (2015). Hepcidin and erythropoietin level in sickle cell disease. *British Journal of Medicine and Medical Research*, *8*(3), 261-265.
28. Madigan, C. and Malik, P. J. E. r. i. m. m. (2006). Pathophysiology and Therapy for Haemoglobinopathies; Part I: Sickle Cell Disease. **8(9):** 1-23.
29. Adewoyin, A. S. J. A. (2015). Management of Sickle Cell Disease: A Review for Physician Education in Nigeria (Sub-Saharan Africa). **2015:**

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ONLINE ISSN: 2992-5797
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30. Aloh, G. S., Obeagu, E. I., Okoroiwu, I. L., Odo, C. E., Chibunna, O. M., Kanu, S. N., ... & Ugwu, G. U. (2015). Antioxidant-Mediated Heinz Bodies Levels of Sickle Erythrocytes under Drug-Induced Oxidative Stress. *European Journal of Biomedical and Pharmaceutical sciences*, *2*(1), 502-507.
31. Odièvre, M.-H., Verger, E., Silva-Pinto, A. C. and Elion, J. J. T. I. j. o. m. r. (2011). Pathophysiological Insights in Sickle Cell Disease. **134(4):** 532.
32. Okwi, A., Byarugaba, W., Parkes, A., Ocaido, M. J. C. i. M. and Health, C. (2010). The Reliability of Sickling and Solubility Tests and Peripheral Blood Film Method for Sickle Cell Disease Screening at District Health Centers in Uganda. **7(1):**
33. Acharya, V., Prakasha, K. J. J. o. E. S. and Review, T. (2019). Computer Aided Technique to Separate the Red Blood Cells, Categorize Them and Diagnose Sickle Cell Anemia. **12(2):**
34. Wajcman, H. and Moradkhani, K. J. T. I. j. o. m. r. (2011). Abnormal Haemoglobins: Detection & Characterization. **134(4):** 538.
35. Kotila, T. R. J. A. o. I. P. M. (2010). Guidelines for Teh Diagnosis of the Haemoglobinopathies in Nigeria. **8(1):** 25-29.
36. Alfirevic, Z., Navaratnam, K. and Mujezinovic, F. J. C. D. o. S. R. (2017). Amniocentesis and Chorionic Villus Sampling for Prenatal Diagnosis. **(9):**
37. Pant, L., Kalita, D., Singh, S., Kudesia, M., Mendiratta, S., Mittal, M. and Mathur, A. J. I. S. R. N. (2014). Detection of Abnormal Hemoglobin Variants by Hplc Method: Common Problems with Suggested Solutions. **2014:**
38. Gupta, P., Kumar, H., Kumar, S. and Jaiprakash, M. J. M. J. A. F. I. (2009). Cation Exchange High Performance Liquid Chromatography for Diagnosis of Haemoglobinopathies. **65(1):** 33-37.
39. Nair, S. B. J. J. o. R. D. R. and Treatment. (2018). Potential Pithfalls in Using Hplc and Its Interpretation in Diagnosing Hbs. **3(3):**
40. Clark, B., Thein, S. J. C. and Haematology, L. (2004). Molecular Diagnosis of Haemoglobin Disorders. **26(3):** 159-176.
41. Li, P., Liu, T., Kamp, D. W., Lin, Z., Wang, Y., Li, D., Yang, L., He, H. and Liu, G. J. M. m. r. (2015). The C-Jun N-Terminal Kinase Signaling Pathway Mediates Chrysotile Asbestos-Induced Alveolar Epithelial Cell Apoptosis. **11(5):** 3626-3634.
42. Waterfall, C. M. and Cobb, B. D. J. N. a. r. (2001). Single Tube Genotyping of Sickle Cell Anaemia Using Pcr-Based Snp Analysis. **29(23):** e119-e119.
43. Tripathi, G. R. J. T. U. J. (2016). A Simplified and Cheapest Method for the Diagnosis of Sickle Cell Using Whole Blood Pcr and Rflp in Nepal. **30(2):** 57-64.
44. Kanter, J., Telen, M. J., Hoppe, C., Roberts, C. L., Kim, J. S. and Yang, X. J. B. m. (2015). Validation of a Novel Point of Care Testing Device for Sickle Cell Disease. **13:** 1-8.
45. McGann, P. T., Schaefer, B. A., Paniagua, M., Howard, T. A. and Ware, R. E. J. A. j. o. h. (2016). Characteristics of a Rapid, Point-of-Care Lateral Flow Immunoassay for the Diagnosis of Sickle Cell Disease. **91(2):** 205-210.
46. Simon, E., Long, B. and Koyfman, A. J. T. J. o. e. m. (2016). Emergency Medicine Management of Sickle Cell Disease Complications: An Evidence-Based Update. **51(4):** 370-381.
47. Chou, S. T. and Fasano, R. M. J. H. O. C. (2016). Management of Patients with Sickle Cell Disease Using Transfusion Therapy: Guidelines and Complications. **30(3):** 591-608.
48. Ware, R. E., Davis, B. R., Schultz, W. H., Brown, R. C., Aygun, B., Sarnaik, S., Odame, I., Fuh, B., George, A. and Owen, W. J. T. L. (2016). Hydroxycarbamide Versus Chronic Transfusion for Maintenance of Transcranial Doppler Flow Velocities in Children with Connor Jr, J. L., Minniti, C. P., Tisdale, J. F. and Hsieh, M. M. J. T. i. j. o. l. e. w. (2017). Sickle Cell Anemia and Comorbid Leg Ulcer Treated with Curative Peripheral Blood Stem Cell Transplantation. **16(1):** 56-59.
49. Sickle Cell Anaemia—Tcd with Transfusions Changing to Hydroxyurea (Twitch): A Multicentre, Open-Label, Phase 3, Non-Inferiority Trial. **387(10019):** 661-670.
50. Ataga, K. I., Kutlar, A., Kanter, J., Liles, D., Cancado, R., Friedrisch, J., Guthrie, T. H., Knight-Madden, J., Alvarez, O. A. and Gordeuk, V. R. J. N. E. J. o. M. (2017). Crizanlizumab for the Prevention of Pain Crises in Sickle Cell Disease. **376(5):** 429-439.
51. Niihara, Y., Miller, S. T., Kanter, J., Lanzkron, S., Smith, W. R., Hsu, L. L., Gordeuk, V. R., Viswanathan, K., Sarnaik, S. and Osunkwo, I. J. N. E. J. o. M. (2018). A Phase 3 Trial of L-Glutamine in Sickle Cell Disease. **379(3):** 226-235.

OPEN ACCESS
ONLINE ISSN: 2992-5797
PRINT ISSN: 2992-6122

52. Vichinsky, E., Hoppe, C. C., Ataga, K. I., Ware, R. E., Nduba, V., El-Beshlawy, A., Hassab, H., Achebe, M. M., Alkindi, S. and Brown, R. C. J. N. E. J. o. M. (2019). A Phase 3 Randomized Trial of Voxelotor in Sickle Cell Disease. **381(6):** 509-519.
53. Yawn, B. P., Buchanan, G. R., Afenyi-Annan, A. N., Ballas, S. K., Hassell, K. L., James, A. H., Jordan, L., Lanzkron, S. M., Lottenberg, R. and Savage, W. J. J. J. (2014). Management of Sickle Cell Disease: Summary of the 2014 Evidence-Based Report by Expert Panel Members. **312(10):** 1033-1048
54. Jordan, L. C., Casella, J. F. and DeBaun, M. R. J. B. j. o. h. (2012). Prospects for Primary Stroke Prevention in Children with Sickle Cell Anaemia. **157(1):** 14-25.
55. Kingwell, K. J. N. r. D. d. (2023). First Crispr Therapy Seeks Landmark Approval.
56. Ezekwe, C. I., Uzomba, C. R., & Ugwu, O. P. C. (2013). The effect of methanol extract of Talinum triangulare (water leaf) on the hematology and some liver parameters of experimental rats. *Global Journal of Biotechnology and Biochemistry*, *8*(2), 51-60.
57. Nwaka, A. C., Ikechi-Agba, M. C., Okechukwu, P. U., Igwenyi, I. O., Agbafor, K. N., Orji, O. U., and Ezugwu, A. L. (2015). The effects of ethanol extracts of Jatropha curcas on some hematological parameters of chloroform intoxicated rats. *American-Eurasian Journal of Scientific Research*, *10*(1), 45-49.
58. Enechi, O. C., Okpe, C. C., Ibe, G. N., Omeje, K. O., and Ugwu Okechukwu, P. C. (2016). Effect of Buchholzia coriacea methanol extract on haematological indices and liver function parameters in Plasmodium berghei-infected mice. *Global Veterinaria*, *16*(1), 57-66.
59. Ezekwe, C. I., Okoro, I. J., Ugwu, P. C., and Ezea, S. C. (2013). The effect of methanol extract of Talinum triangulareon some selected hematological and Kidney parameters of experimental rats. *World J Pharm Pharm Sci*, *2*(6), 4383-4396. Obioma, B. E., Okechukwu, P. U., Emmanuel, I. O., and Ifemeje, J. C. (2014). Antianaemic potential of aqueous leaf extract of Mucuna pruriens on wister albino rats. *Int. J. Curr. Microbiol. App. Sci*, *3*(1), 707-712.
60. Chukwuemeka, I., Utuk, G. S., Ugwu Okechukwu, P. C., Ibiam, U. A., Aja, P. M., and Offor, C. E. (2015). The effect of ethanol leaf extract of Jatropha curcas on some haematological parameters of cyclophosphomide induced anaemia in wister albino rats. *European Journal of Applied Sciences*, 7(1), 17-20
61. Offor, S. C. E., Ukpabi, E. N., Ogbanshi, M. E., Okechukwu, P. U., and Nwali, B. U. (2014). The effects of ethanol leaf-extract of Anacardium occidentale on haemoglobin and packed cell volume of albino rats. *World Journal of Alternative Medicine*, *1*(1), 05-08.
62. Adonu, C. C., Ugwu, O. P., Bawa, A., Ossai, E. C., and Nwaka, A. C. (2013). Intrinsic blood coagulation studies in patients suffering from both diabetes and hypertension. *Int J Pharm Med Bio Sci*, *2*(2), 36-45.
63. Offor, C. E., Okaka, A. N. C., Ogbugo, S. O., Egwu, C. O., and Ugwu, P. C. Effects of ethanol leaf extract of Pterocarpus santalinoides on haemoglobin, packed cell volume and platelets. *IOSR-JNHS 2015; 4: 108, 112.*

CITE AS: Hauwa Ali Buhari, Aisha Sa'ad Ahmad and Emmanuel Ifeanyi Obeagu (2023). Current Advances in the Diagnosis and Treatment of Sickle Cell Anaemia. NEWPORT INTERNATIONAL JOURNAL OF BIOLOGICAL AND APPLIED SCIENCES 4 (1): 1-10. https://doi.org/10.59298/NIJBAS/2023/1.1.11111