JETIR.ORG ISSN: 2349-5162 | ESTD Year : 2014 | Monthly Issue
JOURNAL OF EMERGING TECHNOLOGIES AND INNOVATIVE RESEARCH (JETIR)
An International Scholarly Open Access, Peer-reviewed, Refereed Journal

A Literary Study on Sickle Cell Anaemia (HbS): A Gene Defect Disorder

Dr. Awadhesh Kumar Baranwal [1], Dr. Sujit Kumar[2]

1. Asso. Professor, Department of *Kriya Sharir*, Vivek College of Ayurvedic Sciences and Hospital, Bijnor, Uttar Pradesh
2. Assist. Professor, Department of *Kriya Sharir*, Vivek College of Ayurvedic Sciences and Hospital, Bijnor, Uttar Pradesh
3. **Corresponding Author –** Dr. Awadhesh Kumar Baranwal, Asso. Professor, Department of *Kriya Sharir*, Vivek College of Ayurvedic Sciences and Hospital, Bijnor, Uttar Pradesh

Email id: - drawadhesh2011@gmail.com **Mob: +918004357054**

ABSTRACT:

HbS Sickle Cell Anemia is a homozygous type of Sickle Cell Anemia (HbSS). A single point substitution of valine for glutamine 6 in the -globin chain causes this. This decreases red blood cell solubility, resulting in polymerization and vascular obstruction. The -globin gene is found on the short arm of chromosome 11. When two -globin mutant subunits are joined, haemoglobin S is produced (HbS). In low-oxygen circumstances, the absence of a polar amino acid at the six-point position of the -globin chain promotes non-covalent haemoglobin polymerization, altering the composition and decreasing the flexibility of sickle red blood cells. When normal oxygen voltage is restored, these cells do not return to their original state. As a result, as these compact blood cells travel through small capillaries, they are unable to deform, resulting in artery obstruction and Ischemia. The underlying illness anaemia is caused by hemolysis, or the breakdown of red cells within the spleen.

KEYWORDS: Sickle cell anemia, Genetics disorder, pathophysiology etc.

INTRODUCTION

Sickle cell disease, often known as sickle cell anaemia, is a lifelong blood disorder characterized by red blood cells that take on an uneven, rigid, sickle shape. Sickling causes the cells to become less flexible, which can

lead to a variety of problems. The sickling is caused by a mutation in the haemoglobin gene[1]. Sickle cell disease, which usually affects children, is more common in those who live in tropical and subtropical locations where malaria is prevalent, since plasmodium malaria is stopped from infecting cells by the sides of the cells it infects. Sickle cell disease refers to a range of illnesses that include sickle cell anaemia. Anemia caused by sickle cells is a hereditary disease in which the body fails to deliver oxygen to healthy red blood cells. Flexible, round red blood cells typically move swiftly through blood channels. In sickle cell anaemia, red blood cells form sickles or crescent lunas. Solid, sticky cells can become trapped in microscopic blood arteries, preventing blood and oxygen from reaching vital organs.

MATERIALS AND METHOD

Material about sickle cell anaemia was gathered from a variety of sources, including contemporary textbooks, reputable authoritative blogs, authoritative literature, manuscripts, and more.

HISTORY OF SICKLE CELL ANAEMIA

The disease was first discovered in 1670 in a single Ghanaian family[2,3]. In 1949, Linus Pauling and colleagues were the first to demonstrate that sickle cell disease is caused by a haemoglobin molecule defect. This was the first time a genetic illness was linked to a single protein mutation, a watershed moment in molecular biology, and it was reported in their paper, Sickle Cell Anaemia, a Molecular Disease.

CLASSIFICATION OF SICKLE CELL ANAEMIA

The most common form of sickle cell anaemia is homozygous HbS inheritance. The co-inheritance of HbS and HbC, also known as HbSC, is the second most frequent form of sickle cell anaemia. It is most common in Western Africa, particularly Burkina Faso and Mali, as well as coastal nations like Ghana, Benin, and Western Nigeria.[4,5,6] are the numbers. The sickle thalassemia genotype (HbS/o or HbS/+) is the consequence of thalassemia co-inheritance. Depending on the genetic lesion of the thalassemia component, the clinical manifestation might be minor or as severe as homozygous sickle cell anaemia (HbS/HbS)[7]. When compared to homozygous SS patients, HbS/o-thalassemia patients have a more serious illness course, whereas HbS/+-thalassemia-dependent children of -globin mutation have a variety of phenotypes ranging from intermediate to severe Sickle Cell disorder phenotypes[8], [9].

PATHOPHYSIOLOGY

The pathophysiology of sickle cell anaemia. When exposed to deoxygenated conditions, red blood cells that generate HbS or HbS in combination with other irregular -alleles polymerize and become rigid[10]. Because of their high density, RBC rigid are sensitive to hemolysis and can impair blood supply and endothelial wall integrity[11, 12, 13].

Stable haemoglobin is reorganized into a new shape during deoxygenation, allowing carbon dioxide molecules to attach and revert to normal when released[14]. HbS, on the other hand, continues to polymerize

into hard insoluble strands, which are gel-like substances that are made up of Hb crystals. During acute sickling, intravascular hemolysis results in free haemoglobin in the serum, whereas RBC acquire Na+ and Ca2+, resulting in K+ depletion[15,16,17]. Erythrocyte lyses cause a rise in extracellular haemoglobin, which increases affinity and binding to accessible nitric oxide or nitric oxide precursors, lowering its levels and resulting in vasocoele formation.

GENETICS OF SICKLE CELL ANAEMIA

Fibers can produce haemoglobin protein due to a single amino acid change. Endo nuclease restriction experiments revealed geographic areas of the sickle cell genome[18]. These variants are known as Cameroon, Senegal, Benin, and Saudi-Asian. Their clinical significance stems from the fact that some types, such as those from Senegal and Saudi Arabia, are linked to greater HbF levels and appear to be milder[19]. Because the normal genotype is capable of producing over 50% of the haemoglobin, polymerization problems are minor in persons heterozygous for HbS. Sickle cell disease is caused by the substitution of valine for glutamic acid, the seventh amino acid (if we count the original methionine) in order to change its structure and function[20]. The gene defect is a single nucleotide (A to T) mutation in the p-globin gene that causes glutamate to be replaced by valine at position 6. Haemoglobin S with this mutation is referred to as HbS, as opposed to normal adult HbA.

A single nucleotide mutation, from a GAG to a GTG codon, is responsible for the genetic abnormality. This is usually a minor mutation that has no discernible consequences on hemoglobin's primary, secondary, or quaternary structure. The deoxy version of haemoglobin has a hydrophobic patch on the protein between the E and F helices. Hydrophobic valine residues may be linked with the hydrophobic patch at position 6 of the beta chain in haemoglobin, allowing haemoglobin S molecules to collect and form fibrous precipitates[21].

INHERITANCE OF SICKLE CELL ANAEMIA

Sickle cell anaemia is inherited in the same way as blood colour, hair texture, skin colour, and other physical characteristics are. The amount of haemoglobin in a person's red blood cells is determined by the haemoglobin genes inherited from his or her ancestors.

CLINICAL SIGNS

Sickle cell anaemia is defined by protein symptoms ranging from acute widespread pain to early onset stroke, leg ulcers, and the danger of premature mortality owing to multi-organ failure[22]. Clinical characteristics do not appear until the middle to second year after birth as a result of HbF's impact, by which time it has mostly migrated to adult haemoglobin.

VASO-OCCLUSIVE PAIN

Pain is a central feature of sickle cell anaemia, and it is characterized by unpredictable, episodic nature, and has been regarded as one of the most exaggerated forms of pain seen by humans. Microvascular obstruction causes inflammation of the nociceptive nerve fibers, which causes pressure. Some signs and symptoms include:

- discomfort
- necrosis
- oedema
- Ischaemia
- organ damage[23]

'Hand-foot syndrome,' caused by vaso-occlusion of post-capillary vasculature, resulting in tissue oedema and extremities discomfort, is one of the cardinal features in the first year of existence. [24, 25].

ANAEMIA

The most common sign of sickle cell anaemia is symptomatic anaemia, which is more common in sickle cell anaemia, which has the lowest quantity of haemoglobin in double heterozygous situations. The pace of decline from a person's steady-state haemoglobin level, on the other hand, might produce hypoxia or shock-like symptoms[26, 27.]

ACUTE APLASTIC CRISIS

In sickle cell anaemia and other haemolytic diseases, parvovirus B1928 is the most common cause of acquired bone marrow failure. In children with HbAA who are generally unaffected, there is a modest drop in hematocrit, but in sickle cell anaemia, the lifespan of RBC is shortened to around 10–20 days, resulting in a significant fall in haemoglobin concentration. [29,30.]

SPLENIC REQUISITIONING CRISIS

The main role of the spleen is to remove faulty red blood cells, such as sickled red blood cells (sRBCs), which causes more hemolysis[31]. The increased blood flow to the spleen reduces oxygen stress and strengthens HbS polymerization. As a result of the small capillaries in the splenic vascular bed, more hypoxia develops as a result of RBC polymerization and trapping of afflicted blood cells. This causes hypoxia, RBC polymerization, and inadequate blood flow, causing the spleen to enlarge. It can also happen spontaneously inside the vascular bed in the blood stream, resulting in shock and circulatory failure for unknown reasons. [32].

PSYCHOSOCIAL EFFECT

Sickle cell anaemia has a significant psychological impact on patients and their families[33]. This stems mostly from the impact of pain and symptoms on their personal life, as well as society's perceptions of them. Because of ideas and practices, cultural impacts are extremely significant in these situations. [34,35].

GROWTH AND DEVELOPMENT

According to Platt et al.,[36], children with sickle cell disease show noticeable growth delay by the age of two, which affects weight rather than height, and there may not be a substantial gender discrepancy. Normal height is attained by adulthood, although weight stays lower than the controls. Skeletal maturation is also delayed. [37].

NEUROLOGICAL COMPLICATIONS

In 25 percent of sickle cell disease patients[38], neurological complications include transient ischaemic attacks, brain infarction, cerebral haemorrhage, strokes, unexplained paralysis, spinal cord infarction or compression, central nervous system inflammation, vestibular dysfunction, and auditory hearing loss.

HEPATOBELIARY COMPLICATIONS

Histological examination of the liver reveals centrilobular parenchymal atrophy, bile pigment, periportal fibrosis, haemosiderosis, and cirrhosis.[39]

OCULAR COMPLICATIONS

Ophthalmologic issues include anterior chamber ischaemia, conjunctival vascular tortuosity, retina artery blockage, proliferative retinopathy, retinal detachment, and haemorrhage[40]. Regular retinal testing is part of standard healthcare treatment for sickle cell disease patients.

BONE COMPLICATIONS

The recurring tower skull, bossing of the forehead, and fish mouth deformity of the vertebrae are the result of expanded hematopoietic marrow producing spreading of medullary space, weakening of trabeculae and cortices, and osteoporosis[41]. The increasing pain of bone infarction in 'hand-foot syndrome,' which starts around the age of 12 years, is always the initial sign of sickle cell disease[42,43]. Periarticular infarction or gouty arthritis can cause arthritic pain, edema, and effusion.

DERMATOLOGIC COMPLICATIONS

Leg ulcers develop in sickle cell disease individuals as early as their teenage years. They generally appear around the lateral or medial malleoli and can become recurring and disabling. It's possible that tissue necrosis plays a role in their aetiology. It is more common in men, those with more severe anaemia, and those with lower HbF levels.

Leg ulcers are still treated with cleansing, debridement, and topical antibiotics. Leg edema delays the healing of ulcers and can be addressed with elastic bands or leg elevation.

CARDIAC COMPLICATIONS

Sickle cell anaemia is a kind of sickle cell disease that affects High cardiac output compensates for anaemia, resulting in persistent chamber enlargement and cardiomegaly in many young children. Despite the fact that a patient with sickle cells has a restricted ability for activity, congestive heart disease is uncommon, and mobility restrictions are rarely necessary. During fluid overload, transfusion, reduced oxygen carrying capacity, or hypertension, age-dependent cardiac reserve loss[44] increases the risk of heart failure in older patients. [45].

DIAGNOSIS OF SICKLE CELL ANAEMIA

In HbSS, the falling blood count (FBC) reveals low haemoglobin levels and a high reticulocyte count of 6-8g/dl. Hb levels are often greater in sickle cell disease than in other forms of sickle cell illness. The sickling of red blood cells on a blood film can be produced by adding sodium meta bisulfite. The' sickle solubility test' can also be used to demonstrate the presence of sickle haemoglobin. A combination of hemoglobin's (HbS) produces a muddy appearance in a reduction solution (such as sodium dithionite), whereas standard Hb produces a smooth solution.

TREATMENT AND MANAGEMENT

Expert haemoglobinopathy teams in the United Kingdom manage comprehensive sickle cell anaemia treatment[46]. These teams play an essential role in providing information on sickle cell anaemia to patients and their families, as well as guiding therapy for diseases, psychological entry, social, and health services.

SUPPORTIVE MAINTENANCE

Because sickness, exposure to the cold, or dehydration can worsen pain, prompt treatment ensures that the underlying diseases are given all of the medications they require. Basic devices like incentive spirometry may be useful in preventing problems like acute chest syndrome. Longer-term infection prevention varies by area, but can include vaccines and penicillin prophylaxis[47, 48, 49, 50, 51].

OXYGEN

In the steady state, patients with SS disease have reduced arterial oxygen saturation, and this might fall much lower during acute sickness, particularly acute chest syndrome. In these circumstances, large doses of inspired oxygen can only be beneficial[52].

BLOOD TRANSFUSION

When a person's haemoglobin falls significantly below his or her baseline, and the resulting deficit in the delivery of oxygen to bodily tissues spreads additional deoxygenated Hb sickling, transfusions are given to rectify the anaemia. Red cell aplasia induced by Parvovirus B19 infection, acute splenic sequestration, and crisis hyperhaemolysis[53] are all examples.

BONE MARROW TRANSPLANTATION

Bone marrow transplantation is the only current cure for sickle cell anaemia, and it is one of the most recent therapeutic choices accessible. The researchers discovered a 91 percent event-free survival rate and a death rate of less than 5%. Graft-versus-host-disease, a new leukocyte-producing bone marrow that attacks host tissue cells, is one of the biggest risks of BMT. The skin, kidneys, gastrointestinal tract, and eyes are among the affected tissues, and symptoms include tiredness, weight loss, and jaundice. Graft-versus-host disease is more likely if the donor and recipient are not connected or if there is a disparity in HLA types; methods for meticulous post-transplant immunosuppression may reduce the likelihood of Graft-versus-host-disease[54].

DISCUSSION AND CONCLUSION

This is due to a single-point replacement of glutamine with valine at position 6 of the - globin chain. This decreases red cell solubility, which leads to vascular polymerization and blockage. Under low oxygen circumstances, the absence of a polar amino acid at position six of the -globin chain enables non-covalent haemoglobin polymerization, distorting red blood cells into a sickle shape and reducing their flexibility. Prior to marriage, the prospective pair should get proper and suitable counselling, and genetic counselling for haemoglobin and education should be incorporated in the curriculum of pupils.

***Source of support**: Nil*

***Conflict of interest:** None Declared.*

REFERENCES

1. Platt OS, Brambilla DJ, Rosse WF; Mortality in Sickle Cell Disease. Life Expectancy and Risk Factors for Early Death. N. Engl J Med, 1994; 330 (23): 1639-1644.
2. Konothy Ahulu FD; Effect of Environment on Sickle Cell Disease in West Africa; Epidemiological and Clinical Considerations, 2004.C.V. Mosby Co, St. Louis.
3. Desai DV, Hiren D; Sickle Cell Disease. History and Origin. The Internet Journal of Hematology, 2004; 1(2).
4. Weatherall, D.J. The inherited diseases of hemoglobin are an emerging global health burden. *Blood* **2010**, *115*, 4331–4336.
5. Ansong, D.; Akoto, A.O.; Ocloo, D.; Ohene-frempong, K. Sickle Cell Disease: Management Options and

Challenges in Developing Countries. *Mediterr. J. Hematol. Infect. Dis.* **2013**, *5*, e2013062.

6. Piel, F.B.; Steinberg, M.H.; Rees, D.C. Sickle Cell Disease. *N. Engl. J. Med.* **2017**, *376*, 1561–1573.
7. Steinberg, M.H. Genetic etiologies for phenotypic diversity in sickle cell anemia. *Sci. World J.* **2009**, *9*, 46–67.
8. Ingram, V.M. Anecdotal, Historical and Critical Commentaries on Genetics Sickle-Cell Anemia Hemoglobin: The Molecular Biology of the First "Molecular Disease"—The Crucial Importance of Serendipity. *Genetics* **2004**, *167*, 1–7.
9. De Montalembert, M. Management of children with sickle cell anemia: A collaborative work. *Arch. Pediatr.* **2002**, *9*, 1195–1201.
10. Gardner, R.V. Sickle Cell Disease: Advances in Treatment. *Ochsner J.* **2018**, *18*, 377–389.
11. Manwani, D.; Frenette, P.S. Vaso-occlusion in sickle cell disease: Pathophysiology and novel targeted therapies. *Blood* **2013**, *122*, 3892–3898.
12. Hebbel, R.P. Ischemia-reperfusion injury in sickle cell anemia: Relationship to acute chest syndrome, endothelial dysfunction, arterial vasculopathy, and inflammatory pain. *Hematol. Oncol. Clin. North Am.* **2014**, *28*, 181–198.
13. Sebastiani, P.; Nolan, V.G.; Baldwin, C.T.; Abad-Grau, M.M.; Wang, L.; Adewoye, A.H.; McMahon, L.C.; Farrer, L.A.; Taylor, J.G.; Kato, G.J.; et al. A network model to predict the risk of death in sickle cell disease. *Blood* **2007**, *110*, 2727–2735.
14. Frenette, P.S.; Atweh, G.F. Sickle cell disease: Old discoveries, new concepts, and future promise *J. Clin. Investig.* **2007**, *117*, 850–858.
15. Piel, F.B.; Steinberg, M.H.; Rees, D.C. Sickle Cell Disease. *N. Engl. J. Med.* **2017**, *376*, 1561–1573.
16. Akinsheye, I.; Alsultan, A.; Solovieff, N.; Ngo, D.; Baldwin, C.T.; Sebastiani, P.; Chui, D.H.; Steinberg, M.H. Fetal hemoglobin in sickle cell anemia. *Blood* **2011**, *118*, 19–27.
17. Bonds, D.R. Three decades of innovation in the management of sickle cell disease: The road to understanding the sickle cell disease clinical phenotype. *Blood Rev.* **2005**, *19*, 99–110.
18. De Montalembert, M. Management of children with sickle cell anemia: A collaborative work. *Arch. Pediatr.*
2002, *9*, 1195–1201.
19. Hofiitchter J, Ross PD, Eaton WA.; Super saturation in Sickle Cell Haemoglobin Solutions. Proc. Natl. Acad. Sci. U.S.A, 1976; 73: 3035.
20. Green NS, Fabry ME, Kaptus - Noche L, Nagel RL; Senegal Haplotype is Associated with Higher HbF than Benin and Cameron Haplotypes in African Children with Sickle Cell Anaemia Am, J.Haematol, 1993; 44(2): 145 - 145.
21. Edelstin SJ; Molecular Topology in Crystals and Fibres of Haemoglobin. S.J. MoL Biol; 1981; 150: 557.
22. Watson, R.J.; Burko, H.; Megas, H.; Robinson, M. The hand-foot syndrome in sickle-cell disease in young children. *Pediatrics* **1963**, *31*, 975–982.
23. Piel, F.B.; Tewari, S.; Brousse, V.; Analitis, A.; Font, A.; Menzel, S.; Chakravorty, S.; Thein, S.L.; Inusa, B.; Telfer, P.; et al. Associations between environmental factors and hospital admissions for sickle cell

disease. *Haematologica* **2017**, *102*, 666–675.

24. Ballas, S.K.; Kesen, M.R.; Goldberg, M.F.; Lutty, G.A.; Dampier, C.; Osunkwo, I.; Wang, W.C.; Hoppe, C.; Hagar, W.; Darbari, D.S.; et al. Beyond the Definitions of the Phenotypic Complications of Sickle Cell Disease: An Update on Management. *Sci. World J.* **2012**, *2012*, 949535.
25. Brousse, V.; Buffet, P.; Rees, D. The spleen and sickle cell disease: The sick (led) spleen. *Br. J. Haematol.* **2014**,

166, 165–176.
26. Minhas, P.S.; KVirdi, J.; Patel, R. Double whammy-acute splenic sequestration crisis in patient with aplastic crisis due to acute parvovirus infection. *J. Commun. Hosp. Int. Med. Perspect.* **2017**, *7*, 194–195.
27. Inati, A. Recent advances in improving the management of sickle cell disease. *Blood Rev.* **2009**, *23*, S9–S13.
28. Minhas, P.S.; KVirdi, J.; Patel, R. Double whammy-acute splenic sequestration crisis in patient with aplastic crisis due to acute parvovirus infection. *J. Commun. Hosp. Int. Med. Perspect.* **2017**, *7*, 194–195.
29. Rezende, P.V.; Viana, M.B.; Murao, M.; Chaves, A.C.; Ribeiro, A.C. Acute splenic sequestration in a cohort of children with sickle cell anemia. *J. Pediatr. (Rio J.)* **2009**, *85*, 163–169.
30. Araujo, A.N. Acute splenic sequestration in children with sickle cell anemia. *J. Pediatr. (Rio J.)* **2009**, *85*, 373–374.
31. Mulder, N.; Nembaware, V.; Adekile, A.; Anie, K.A.; Inusa, B.; Brown, B.; Campbell, A.; Chinenere, F.; Chunda-Liyoka, C.; Derebail, V.K.; et al. Proceedings of a Sickle Cell Disease Ontology workshop—Towards the first comprehensive ontology for sickle cell disease. *Appl. Transl. Genom.* **2016**, *9*, 23–29.
32. Hsu, L.L.; Green, N.S.; Ivy, E.D.; Neunert, C.E.; Smaldone, A.; Johnson, S.; Castillo, S.; Castillo, A.; Thompson, T.; Hampton, K.; et al. Community health workers as support for sickle cell care. *Am. J. Prev. Med.* **2016**, *51*, S87–S98.
33. Ohaeri, J.U.; Shokunbi, W.A. Psychosocial burden of sickle cell disease on caregivers in a Nigerian setting. *J. Natl. Med. Assoc.* **2002**, *94*, 1058.
34. Sickle Cell Society. Standards for the Clinical Care of Adults with Sickle Cell Disease in the UK—2018. Available online: https://www.sicklecellsociety.org/sicklecellstandards/ (accessed on 10 Fbruary 2019).
35. Dampier, C.; LeBeau, P.; Rhee, S.; Lieff, S.; Kesler, K.; Ballas, S.; Rogers, Z.; Wang, W.; Comprehensive Sickle Cell Centers (CSCC) Clinical Trial Consortium (CTC) Site Investigators. Health-related quality of life in adults with sickle cell disease (SCD): A report from the comprehensive sickle cell centers clinical trial consortium. *Am. J. Hematol.* **2011**, *86*, 203–205.
36. Lebensburger, J.D.; Miller, S.T.; Howard, T.H.; Casella, J.F.; Brown, R.C.; Lu, M.; Iyer, R.V.; Sarnaik, S.; Rogers, Z.R.; Wang, W.C.; et al. Influence of severity of anemia on clinical findings in infants with sickle cell anemia: Analyses from the BABY HUG study. *Pediatr. Blood Cancer* **2012**, *59*, 675–678.
37. Vichinsky, E.P. Comprehensive care in sickle cell disease: Its impact on morbidity and mortality.

Semin. Hematol. **1991**, *28*, 220–226.
38. Matthews, C.; Walton, E.K.; Inusa, B. Sickle cell disease in childhood. *Stud. BMJ* **2014**, *22*.
39. Danaee, A.; Inusa, B.; Howard, J.; Kesse-Adu, R.; Robinson, S. hyperhaemolysis in patients with

haemoglobinopathies: A single centre experience: 229. *Br. J. Haematol.* **2014**, *165*, 96.

40. Heyman MB, Vischinsky E, Katz R; Growth Retardation in Sickle Cell Disease Treated by Nutritional Support. Lancet, 1985; 1: 903.
41. Sarnaik AS, Lusher J.M; Neurological Complications of Sickle Cell Anaemia, Am. J. Pediatr. HaematoL Oncol, 1982; 4: 386.
42. Wagner G, Johnson R, Claster S; Gynecological and Obstetrical Complications in Sickle Cell Disease. In Sickle Cell Disease: Progress and Prospects. National Sickle Cell Disease Programme. Boston, 1986.
43. Hayes RJ, Condon PI, Serjeant GR; Haematologic Factors Assocaited with Proliferative Retinopathy in Homozygous Sickle Cell Disease. Br. J. Ophthalmol; 1981; 65: 29.
44. Diggs LW; Bone and Joint Lesions in Sickle Cell Disease. Clin. Orthop, 1967; 52; 119.
45. Stevens MC, Pad wick M, Serjeant GR Observations on the Natural History of Dactylistis in Homozygous Sickle Cell Disease. Clin.Pediatr. (Phila), 1981; 20: 311.
46. Steinberg ME, Steinberg DR; Evaluation and Staging of Avascular Necrosis. Semin. Arthroplasty, 1991; 2: 175.
47. Val - Mejias, J, Lee WK, Weisee AB, Regan TJ; Left Ventricular Performance During and After Sickle Cell Crisis. AM. J.Heart; 1979; 97: 585.
48. Gerry JL, Bulkley BH, Hutchins GM; Clinical Analysis of Cardiac Dysfunction in 52 Patients with Sickle Cell Anaemia, Am. J.Cardiol, 1978; 42: 211.
49. Waley MA; Chemoprophylaxis of Homozygous Sicklers with Antimalaria and Long Acting Penicillin. Br. Med. J; 1965; 12: 86.
50. Kassim, A.A.; Sharma, D. Hematopoietic stem cell transplantation for sickle cell disease: The changing landscape. *Hematol. Oncol. Stem Cell Ther.* **2017**, *10*, 259–266.
51. Adewoyin, A.S.; Obieche, J.C. Hypertransfusion therapy in sickle cell disease in Nigeria. *Adv. Hematol.* **2014**, *2014*, 923593.
52. Wiebking, V.; Hütker, S.; Schmid, I.; Immler, S.; Feuchtinger, T.; Albert, M.H. Reduced toxicity, myeloablative HLA-haploidentical hematopoietic stem cell transplantation with post-transplantation cyclophosphamide for sickle cell disease. *Ann. Hematol.* **2017**, *96*, 1373–1377.
53. Hashmi, S.K.; Srivastava, A.; Rasheed, W.; Adil, S.; Wu, T.; Jagasia, M.; Nassar, A.; Hwang, W.Y.; Hamidieh, A.A.; Greinix, H.T.; et al. Cost and quality issues in establishing hematopoietic cell transplant program in developing countries. *Hematol. Oncol. Stem Cell Ther.* **2017**, *10*, 167–172.
54. Inusa, B.P.; Anie, K.A.; Lamont, A.; Dogara, L.G.; Ojo, B.; Ijei, I.; Atoyebi, W.; Gwani, L.; Gani, E.; Hsu, L. Utilising the 'Getting to Outcomes®' Framework in Community Engagement for Development and Implementation of Sickle Cell Disease Newborn Screening in Kaduna State, Nigeria. *Int. J. Neonatal Screen.* **2018**, *4*, 33.