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Introductory Chapter: Introduction to the History, Pathology and Clinical Management of Sickle Cell Disease

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1. Introduction

Sickle cell disease (SCD) is due to a single point mutation (Glub6Val) that causes polymerisation of the mutant hemoglobin (Hb) S, resulting in sickling of erythrocytes [1]. Inflammation, haemolysis, microvascular obstruction and organ damage characterise the clinical expression of SCD, which is highly variable in individual patients. Environmental and multiple genetic factors modify many aspects of SCD and therefore contribute to the clinical variability [2, 3].

This chronic, complex and monogenetic haematological condition that leads to haemolytic anaemia, severe acute complications and chronic organ damage was formally reported in 1910 [4]. One hundred years after Herrick's initial report, there have been significant advances in the diagnosis and management [5].

Forty years ago only half of children with sickle cell anaemia were expected to reach adulthood [6]. However, advances in the diagnosis and management of SCD have improved the survival and quality of life significantly. Recent figures suggest survival of 53 years for men and 58.5 years for women [7, 8] and over 94% surviving to adulthood [8, 9].

SCD is now one of the most common genetic disorders in the world with high prevalence in sub-Saharan Africa (SSA), the Middle East, the Mediterranean and the Indian subcontinent [1, 10, 11]. In the United States, almost 1 in 10 African Americans has the sickle cell trait, with 1 in 600 being homozygous for the sickle hemoglobin allele [12, 13]. In the UK, it is diagnosed at birth, through routine Newborn screening with incidence of about 1 in every 2000 births [3, 14]. However despite the high prevalence in sub-Saharan Africa (SSA) essential public health programmes have not been implemented due to limited medical resources and infrastructures [10, 11, 15, 16]. As a consequence, infant and childhood mortality due to SCD remains high. It is estimated that without intervention, up to 50-90% of affected infants may die by 5 years of age from SCD [11, 15, 17, 18]. While high regional disease prevalence would

be expected to facilitate epidemiologic, translational and clinical research, the majority of SSA countries lack the capacity to provide the comprehensive care for SCD [11].

2. Early description

James Herrick is widely acknowledged as the first physician to describe a case of sickle cell. However, the term 'sickle cell anaemia' was not coined until 1922 [19], when a review of the first four cases of the disease was conducted, including that described by Herrick [20, 21].

However, it is argued that case reports, up to 60 years prior to that by Herrick, may have described sickle cell disease [6, 17]. A post-mortem, performed in 1898, of a patient who died in hospital after being admitted for pains, jaundice and previous leg ulcers shows that these symptoms are suggestive of SCD [22]. It has also been proposed that the clinical illness had been previously recognised in Africa as "cold-season rheumatism" and that the possibility of genetic inheritance of the illness had even been noted [10].

3. Discovery of molecular and genetic basis

It was not until 40 years after the first description of sickle cell anaemia that a homozygous pattern of inheritance was confirmed simultaneously by two separate studies, one a pedigree study in Africa [11, 12]. These studies demonstrated that sickle cell anaemia was inherited in an autosomal recessive pattern. In the late 1940s, Pauling discovered that blood from sickle cell patients had differing mobility during electrophoresis [23, 24]. This indicated that there were chemical differences between the hemoglobin of the different cells. Thus, Pauling and colleagues proposed that sickle cell anaemia was a molecular disease, the first disease of this kind [23].

Vernon Ingram was to be the discoverer of the exact difference between sickle cell and normal adult hemoglobin. Ingram identified that sickle hemoglobin (HbS) was more positively charge hemoglobin A (HbA) [21, 25]. The amino acid sequence of hemoglobin was shown to differ by only one substitution of glutamic acid with valine in the β chain of HbS [26]. As knowledge of the pathophysiology of SCD is a complex phenomenon between vaso-occlusion and hemolysis [27–29].

4. Prophylactic penicillin and pneumococcal vaccination

Studies have shown that infant mortality is particularly high in sickle cell disease. Scott's observations revealed that the number of children reaching adulthood was only approximately 50% [4] in the 1960s. The Cooperative Study of Sickle Cell Disease (CSSD) has shown that the peak incidence of death was between the ages of 1 and 3 [30]. Furthermore, the CSSD showed that the largest killer in SCD was infection, with this being the cause of death in 50% of subjects being followed below the age of 20 [20]. Infection was also shown to be a predominant factor in

other studies of mortality [21, 22] with pneumococcal disease being identified as a major killer [19, 20]. It has even been calculated that the risk of developing meningitis from *Streptococcus pneumoniae* is 30 times more likely in the sickle cell population than in the general population [23].

The increased risk of infection may be attributed to many factors, including decreased immuno-globulin function, poor cell-mediated immunity and reduced opsonisations [24–27]. Importantly, there is a decrease in splenic function as a result of microvascular occlusions and infarctions [24]. The decrease in immune function leads to a vulnerability to encapsulated organisms particularly *Streptococcus pneumoniae, Haemophilus influenzae* type B and *Salmonella* [28].

Following the recognition of infection playing a major role in the disease, a study commencing in 1983 showed the benefit of prophylactic penicillin. Gaston and colleagues recruited sickle cell patients under the age of 3 to a randomised control study to determine if daily prophylactic penicillin would be effective at reducing childhood infections. Astonishingly it was found to reduce septicaemia by 84% and the trial was terminated early. The Penicillin Prophylaxis in SCD study (PROPS) therefore recommended that all children should be screened and started on penicillin by the time they reached 4 months of age [31].

In addition to prophylactic antibiotics, pneumococcal vaccination has also become an important part of sickle cell management. Those immunised had lower incidence of pneumococcal septicaemia than the control group [32, 33]. The introduction of new conjugated vaccines against other encapsulated bacteria (13 strains of *Streptococcus pneumoniae*; *Meningococcus* A, C, W, Y and B and *Haemophilus influenzae*) has reduced the rate of pneumococcal bacteraemia by 93.4% in children aged <5 years to 134 cases per 100,000 person-years, P<0.001 [33–35]. Incidence of invasive pneumococcal disease among individuals with sickle cell disease before and after the introduction of the pneumococcal conjugate vaccine [32, 35].

5. Prenatal and Neonatal SCD Screening

SCD is associated with high infant mortality rate; therefore, early preventive intervention is essential in reducing these deaths [14, 36]. A maternal blood screen during or preceding pregnancy seems the most cost-effective method of initiating a screening programme, as if the mother does not carry the sickle allele, then there is no risk of the child having sickle cell disease and additionally this initial screen does not need repetition for future pregnancies. If maternal screening reveals a sickle cell trait or SCD, the father can be invited for investigation [14, 36].

Since 1978 it has been possible to obtain foetal DNA to diagnose sickle cell disease prenatally [18], via amniocentesis or chorionic villus sampling (CVS). CVS offers the advantage that the family is given the choice early in pregnancy. Prior to this it was only possible to diagnose sickle cell disease via direct viewing of foetal blood. In some countries it has been in use for national screening programmes and rates of termination of pregnancy are as high as 74% in Cuba [37–40].

The importance of neonatal identification of SCD is emphasised [36, 41, 42].

By 1994 the majority of United States cities had implemented universal neonatal hemoglobinopathy screening [12, 43]; the UK has only fully implemented its universal sickle cell screening programme in the last few years [14, 44]. In Africa, only Ghana and the Republic of Benin have established selective and pilot Newborn screening programme, respectively [37, 41, 45, 46].

5.1. Pain management

The clinical severity of SCD is variable and usually defies genetic or phenotypic explanation. The cooperative study of the natural history of sickle cell disease showed that about 5% of patients accounted for one-third of hospital days devoted to pain control [19]. Acute VOC and chronic pain syndrome could be disabling to the patient, and studies have demonstrated an association of acute pain syndromes with other complications of SCD, including death [19, 47].

Pain management guidelines and the need to rule out life-threatening comorbidities suggest the need for rapid physician evaluation of patients who present to the emergency department (ED) with complaints related to SCD [47]. The American Pain Society guidelines recommend initial assessment and analgesia within 30 min of arrival [5, 48].

5.2. Hydroxyurea (HU)

From the difficulty in identifying sickle-shaped erythrocytes in neonates, Janet Watson postulated, in 1948, that high fetal hemoglobin leads to a decrease in cells that could sickle and therefore a decrease in sickle hemoglobin in those red blood cells [49]. Several years later it was suggested that by increasing or prolonging the concentration of foetal hemoglobin in erythrocytes, it would be possible to decrease the frequency and severity of the clinical manifestations of SCD [50–52].

HU, an anti-leukaemia agent with the capacity to increase foetal Hb, was introduced to treat sickle cell disease with significant clinical and symptomatic improvement. In 1992 a randomised double-blind study, the Multicentre Study of HU in Sickle Cell Anaemia (MSH), showed that this new drug could decrease episodes of painful crises, acute chest syndrome and the need for transfusion [53, 54]. The study recruited 299 adults with more than three painful crises in the year prior to the start of HU, and the clinical effect was great enough for the trial to terminate 3 months early [54, 55].

The paediatric studies on the use of hydroxyurea reflected the results of the adult trials, with reduced acute complications and with no toxicity or decreased growth, and suggested reduced end organ damage if administered early [56–58].

6. Stroke and stroke prevention

Stroke is an important cause of morbidity and mortality of SCD with an estimated 11% having had a stroke by the age of 20 [59]. Although the treatment of strokes in SCD had been

improving, it was a ground breaking trial in the final decade of the twentieth century that changed the way SCD was monitored [60, 61] to prevent stoke in this group of patients.

Landmark's work into the use of transcranial Doppler (TCD) ultrasounds showed that severe sickle cell disease could lead to the narrowing of cerebral blood vessels. These would appear on ultrasonography as increased flow in that region and patients with abnormal flow are at increased risk of stroke [60, 62]. Silent cerebral infarcts are the most common neurologic injury in children with sickle cell anaemia and are associated with the recurrence of an infarct (stroke or silent cerebral infarct), and regular blood transfusion therapy significantly reduced the incidence of the recurrence of cerebral infarct in children with sickle cell anaemia by 58% [63, 64].

7. Pulmonary hypertension

Pulmonary hypertension (PAH) is recognised to be a common complication of SCD and other haemolytic disorders and is associated with increased mortality and morbidity. Retrospective studies suggest a prevalence of PAH ranging from 20 to 40% [65, 66] among adults, and a prospective study showed that prevalence of PAH in paediatric population is 31%, and the two-year mortality rates approach 50% [65, 66].

Chronic hemolysis represents a prominent mechanistic pathway in the pathogenesis of SCD-associated PAH via a nitric oxide (NO) scavenging and abrogation of NO salutatory effects on vascular function. These processes lead to acute and chronic pulmonary vasoconstriction [65]. Many known infectious risk factors for PAH, i.e. human immunodeficiency virus (HIV) infection, chronic hepatitis B and C viral infections and possibly malaria, are hyper endemic in African countries where the prevalence of SCD is very high. Interactions between these infectious complications and SCD-related hemolysis could yield an even higher incidence of PAH among the African SCD patients.

Self-reported history of cardiovascular and renal complications, systolic hypertension, high lactate dehydrogenase levels (index of haemolysis), high level of alkaline phosphatase, low transferrin concentration (indicating iron overload) and priapism in men were found to be independent correlates of PAH [20, 67].

Therapy for SCD-related PAH remains challenging. Treatment with HU at maximum tolerated dose and judicious use of blood transfusion support and iron-chelating agents where indicated is recommended [66]. While HU is a potential NO donor effect, it has not been shown to impact mortality of SCD-related PAH [51]. There is increasing interest in the use of sildenafil in SCD-related PAH. Sildenafil was well tolerated by both male and female patients and it reduced the estimated pulmonary artery systolic pressure and increased the 6-min walk distance [68, 69].

Gene therapy has the potential to correct the underlying defect leading to the clinical manifestations of sickle cell disease. It would reduce the need for many of the preventative treatments and invasive therapies. A few years ago, this may not have seemed possible; however, gene

therapy has been proven to be effective in mouse models [1, 2], and there are currently several teams working on phase II trials using viral vectors [70–72].

8. Global perspectives

The World Health Organization has estimated that there may be approximately 216,000 babies born with HbSS disease in Africa each year and that the disease may account for 10–20% of neonatal mortality in West Africa, very little is known about the overall global burden of SCD [68].

Although there have been improvements in the management of SCD in developed countries, much less progress has been made in the developing world in which the disease is common, where it is still an important cause of childhood mortality. In low-income countries, basic facilities for management are lacking, systemic screening is not a common practice, and diagnosis is made late.

Research collaborations between sickle cell research groups in rich and poor countries would be of considerable benefit to the health and well-being of patients with SCD in the developing countries. In particular, interactions of this kind offer an opportunity to improve clinical and diagnostic facilities and hence the management of patients in the developing world. We cannot yet cure SCD, but we have learnt that simple interventions significantly improve morbidity and mortality.

9. Conclusion

Although there has been dramatic improvement in the diagnosis, management and monitoring of sickle cell disease over the last century, bone marrow transplantation (BMT) is currently the only cure for SCD with a curative success rate of approximately 90–93% [68, 69]. Conversely, there are severe risks and complications including rejection, marrow aplasia, neurological disorders, graft-versus-host disease and death, and standard BMT is limited by a requirement for human leukocyte antigen (HLA)-matched sibling donors [70]. Currently transplantation is only considered for those children with HLA-identical siblings and in whom the clinical manifestation of the disease does not respond to standard care.

The past 100 years have shown great accomplishments for SCD including newborn screening, penicillin prophylaxis, primary stroke prevention using blood transfusion, stroke prevention trial in sickle cell anaemia (STOP) and controlled trial of transfusions for silent cerebral infarct in sickle cell anaemia. The role of hydroxyurea therapy in adults and children to reduce pain, hospitalisations and most recently as an alternative for controlling cerebral blood velocity—transcranial Doppler (TCD) with Transfusion Changing to Hydroxyurea (TWiTCH) therapy. Although a risk-free cure has not been found in this last and current century, the following 100 years look to be extremely promising for sickle cell anaemia; stem cell transplantation is now more commonly used in SCD.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

MC and NW reviewed the literature and wrote the draft of the manuscript, BI designed, reviewed and made the substantial changes the manuscript. All authors discussed, read and approved the manuscript.

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References

[1] Chakravorty S, Williams TN. Sickle cell disease: a neglected chronic disease of increasing global health importance. Arch Dis Child [Internet]. 2014;100(1):48–53. Available from: http://adc.bmj.com/cgi/doi/10.1136/archdischild-2013-303773

[2] Weatherall DJ. The challenge of haemoglobinopathies in resource-poor countries. Br J Haematol. 2011;(July):736–44.

[3] Modell B, Darlison M, Birgens H, Cario H, Faustino P, Giordano PC, et al. Epidemiology of haemoglobin disorders in Europe: an overview. Scand J Clin Lab Invest. 2007;67(1):39–69.

[4] Noel WC, Senn N, Hek L, Murphy JB, Wil DH, Fenger C, et al. The Rest of the ZO0GJDBDOŒ ^ DDLZÛQDDDE. 2016;4354.

[5] Inati A. Recent advances in improving the management of sickle cell disease. Blood Rev [Internet]. 2009;23(Suppl. 1):S9–13. Available from: http://dx.doi.org/10.1016/S0268-960X (09)70004-9

[6] Modell B. Global epidemiology of haemoglobin disorders and derived service indicators. Bull World Health Organ [Internet]. 2008[cited 2012 Nov 12];2008(6):480–7. Available from: http://www.who.int/bulletin/volumes/86/6/06-036673.pdf

[7] Platt O, Brambilla D, Rosse W, Milner P. Mortality in Sickle Cell Disease. N Engl J Med. 1994;330(23):1639–44.

[8] Quinn CT, Rogers ZR, Buchanan GR. Survival of children with sickle cell disease. Blood [Internet]. 2004 [cited 2012 Oct 25];103(11):4023–7. Available from: http://www. pubmedcentral.nih.gov/articlerender.fcgi?artid=1828870&tool=pmcentrez&rendertype= abstract

[9] Telfer P, Coen P, Chakravorty S, Wilkey O, Evans J, Newell H, et al. Clinical outcomes in children with sickle cell disease living in England: a neonatal cohort in East London. Haematologica [Internet]. 2007 [cited 2013 Feb 19];92(7):905–12. Available from: http:// www.ncbi.nlm.nih.gov/pubmed/17606440

[10] Piel FB, Patil AP, Howes RE, Nyangiri OA, Gething PW, Dewi M, et al. Global epidemi- ology of Sickle haemoglobin in neonates: A contemporary geostatistical model-based map and population estimates. Lancet [Internet]. 2013;381(9861):142–51. Available from: http://dx.doi.org/10.1016/S0140-6736(12)61229-X

[11] Grosse SD, Odame I, Atrash HK, Amendah DD, Piel FB, Williams TN. Sickle cell disease in Africa: a neglected cause of early childhood mortality. Am J Prev Med [Internet]. 2011 [cited 2012 Nov 25];41(6 Suppl. 4):S398–405. Available from: http://www.ncbi.nlm.nih. gov/pubmed/22099364

[12] Angastiniotis M, Modell B. Global epidemiology of hemoglobin disorders. Ann N Y Acad Sci. 1998;850:251–69.

[13] Biswas T. Global burden of sickle cell anaemia is set to rise by a third by 2050. Brtish Med J [Internet]. 2013;4676(July 2013):6638. Available from: http://www.bmj.com/content/347/ bmj.f4676.pdf+html

[14] Streetly A, Latinovic R, Hall K, Henthorn J. Implementation of universal newborn bloodspot screening for sickle cell disease and other clinically significant haemoglobi nopathies in England: screening results for 2005-7. J Clin Pathol [Internet]. 2009;62(1):26– 30. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=2603283 &tool=pmcentrez&rendertype=abstract

[15] Williams TN, Weatherall DJ. World distribution, population genetics, and health burden of the hemoglobinopathies. Cold Spring Harb Perspect Med. 2012;2(9):1–14.

[16] Weatherall DJ. The inherited diseases of hemoglobin are an emerging global health burden. [Internet]. Blood. 2010:4331–6. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=2881491&tool=pmcentrez&rendertype=abstract

[17] Fleming AF. The presentation, management and prevention of crisis in sickle cell disease in Africa. Blood Rev. 1989;3(1):18–28.

[18] Odame I, Kulkarni R, Ohene-Frempong K. Concerted global effort to combat sickle cell disease: The first global congress on sickle cell disease in Accra, Ghana. Am J Prev Med [Internet]. 2011;41(6 Suppl. 4):S417–21. Available from: http://dx.doi.org/10.1016/j.amepre.2011.09.019

[19] Ballas SK, Ballas SK. Defining the Phenotypes of Sickle Cell Disease. 2016;269(August).

[20] Rees DC, Williams TN, Gladwin MT. Sickle-cell disease. Lancet [Internet]. 2010;376 (9757):2018–31. Available from: http://dx.doi.org/10.1016/S0140-6736(10)61029-X

[21] Ingram VM. Abnormal human haemoglobins. I. The comparison of normal human and sickle-cell haemoglobins by fingerprinting. Biochim Biophys Acta [Internet]. 1958;28 (28):539–45. Available from: http://www.sciencedirect.com/science/article/pii/000630025 890516X

[22] Lanzkron S, Carroll CP, Jr CH. Mortality rates and age at death from sickle cell disease: U.S., 1979–2005. Public Heal reports (Washington, DC 1974). 2013;128(2):110–6.

[23] Strasser BJ. Linus Pauling's "molecular diseases": Between history and memory. 2002;93 (2):83–93.

[24] Eaton WA. Linus Pauling and sickle cell disease. Biophys Chem. 2003;100(1–3):109–16.

[25] Ingram VM. A specific chemical difference between the globins of normal human and sickle-cell anaemia haemoglobin. Nature. 1956;178(4537):792–4.

[26] Riggs MG, Ingram VM. Differences in erythrocyte membrane proteins and glycoproteins in sickle cell disease. Biochem Biophys Res Commun [Internet]. 1977;74(1):191–8. Available from: http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=83 6277&retmode=ref&cmd=prlinks\nfile:///Users/Aniradha/Desktop/Dropbox/Papers2/ Library.papers3/Files/FE/FEF819A5-3466-4159-9CF8-8AA03710A3F3.pdf\npapers3:// publication/uuid/E0DE2EAB-

[27] Hebbel RP, Osarogiagbon R, Kaul D. The endothelial biology of sickle cell disease: Inflammation and a chronic vasculopathy. Microcirculation [Internet]. 2004 [cited 2013 Jan 27];11(2):129–51. Available from: http://doi.wiley.com/10.1080/10739680490 278402

[28] Kato GJ. New insights into sickle cell disease. Curr Opin Hematol [Internet]. 2016;23 (3):224–32. Available from: http://content.wkhealth.com/linkback/openurl?sid=WKPTLP: landingpage&an=00062752-201605000-00007

[29] Minniti CP, Delaney KH, Gorbach AM, Xu D, Lee CR, Malik N, et al. NIH Public Access. 2014;89(1):1–6.

[30] Bonds DR. 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(2):99–110.

[31] Gaston MH, Verter JI, Woods G, Pegelow C, Kelleher J, Presbury G, et al. Prophylaxis with oral penicillin in children with sickle cell anemia. N Engl J Med. 1986;314 (25):1593–9.

[32] Cober MP, Phelps SJ, Ohio N. Brief review article penicillin prophylaxis in children with sickle cell disease. 2010;15(3).

[33] Affairs P. Penicillin prophylaxis in children with sickle cell disease. 1991;302(May):1205–6.

[34] Preventing infections in sickle cell disease: The unfinished. 2016;63(5):25911.

[35] Booth C, Inusa B, Obaro SK. Infection in sickle cell disease: A review. 2010:2–12.

[36] Pt M, Sd G, Santos B, V DO, Bernardino L, Nj K, et al. A cost-effectiveness analysis of a pilot neonatal screening program for sickle cell anemia in the Republic of Angola. 2015;3476(15):26477868.

[37] McGann PT, Ferris MG, Ramamurthy U, Santos B, de Oliveira V, Bernardino L, et al. A prospective newborn screening and treatment program for sickle cell anemia in Luanda, Angola. Am J Hematol. 2013;88(12):984–9.

[38] Petrou M, Brugiatelli M, Ward RH, Modell B. Factors affecting the uptake of prenatal diagnosis for sickle cell disease. J Med Genet [Internet]. 1992;29(11):820–3. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=1016180&tool=pmcentrez&rendertype=abstract

[39] Loader S, Sutera CJ, Segelman SG, Kozyra A, Rowley PT. Prenatal hemoglobinopathy screening. IV. Follow-up of women at risk for a child with a clinically significant hemoglobinopathy. Am J Hum Genet. 1991;49(6):1292–9.

[40] Rowley PT, Loader S, Sutera CJ, Walden M, Kozyra A. Prenatal screening for hemoglobinopathies. I. A prospective regional trial. Am J Hum Genet [Internet]. 1991;48(3):439–46. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1682994/\nhttp://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=1682994&tool=pmcentrez&rendertype=abstract

[41] Inusa BP, Juliana Olufunke YD, John Dada L. Sickle cell disease screening in Northern Nigeria: The co-existence of B-thalassemia inheritance. Pediatr Ther [Internet]. 2015;5 (3):3–6. Available from: http://www.omicsonline.org/open-access/sickle-cell-disease-screening-in-northern-nigeria-the-coexistence-of-thalassemia-inheritance-2161-0665-1000262.php?aid=59622

[42] Modell B. Delivering genetic screening to the community. Ann Med. 1997;29(6):591–9.

[43] Vichinsky E, Lubin BH. Suggested guidelines for the treatment of children with sickle cell anemia. Hematol Oncol Clin North Am. 1987;1(3):483–501.

[44] Henthorn JS, Almeida AM, Davies SC. Neonatal screening for sickle cell disorders. Br J Haematol. 2004;124(3):259–63.

[45] Tshilolo L, Aissi LM, Lukusa D, Kinsiama C, Wembonyama S, Gulbis B, et al. Neonatal screening for sickle cell anaemia in the Democratic Republic of the Congo: Experience from a pioneer project on 31 204 newborns. 2009;(fig 1):35–8.

[46] Ohene-frempong K, Oduro J. Screening newborns for sickle cell disease in ghana submitted by Kwaku Ohene-Frempong suppression of the olivocochlear reflex: A neurotoxic adverse effect of vincristine submitted by Helen Kosmidis transplantation for the treatment of thalassemia: The g. 1993;

[47] Colombatti R, Sainati L. Management of children with sickle cell disease in Europe: Current situation and future perspectives. 2016;(July):129–35.

[48] Melorose J, Perroy R, Careas S. Evidence-based management of sickle cell disease. Expert Panel Report, 2014. US Dep Heal Humand Serv NIH. 2015;1.

[49] Ideguchi H. Congenital hemolytic anemia. Nippon Rinsho Jpn J Clin Med. 2005;63:415–9.

[50] Mpalampa L, Ndugwa CM, Ddungu H, Idro R. Foetal haemoglobin and disease severity in sickle cell anaemia patients in Kampala, Uganda. BMC Blood Disord [Internet]. 2012 [cited 2012 Nov 25];12(1):11. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22958547

[51] Saraf SL, Molokie RE, Nouraie M, Sable CA, Luchtman-Jones L, Ensing GJ, et al. Differences in the clinical and genotypic presentation of sickle cell disease around the world. Paediatr Respir Rev. 2014;15(1):4–12.

[52] Rooks Y, Pack B. A profile of sickle cell disease. Nurs Clin North Am. 1983;18:131–8.

[53] Moore RD, Charache S, Terrin ML, Barton FB. Cost-effectiveness of hydroxyurea in sickle cell anemia. 2000;31(January):26–31.

[54] Charache S, Barton FB, Moore RD, Terrin ML, Steinberg MH, Dover GJ, et al. Hydroxyurea and sickle cell anemia. Clinical utility of a myelosuppressive "switching" agent. The multicenter study of hydroxyurea in sickle cell anemia. Medicine (Baltimore). 1996;75 (6):300–26.

[55] Charache S. Mechanism of action of hydroxyurea in the management of sickle cell anemia in adults. Semin Hematol. 1997;34(3 Suppl 3):15–21.

[56] Wang WC, Ware RE, Miller ST, Iyer R V, Casella JF, Minniti CP, et al. Hydroxycarbamide in very young children with sickle-cell anaemia: a multicentre, randomised, controlled trial (BABY HUG). Lancet [Internet]. 2011 [cited 2012 Nov 25];377(9778):1663–72. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3133619&tool=pmcentrez&rendertype=abstract

[57] Hankins JS, Ware RE, Rogers ZR, Wynn LW, Lane PA, Scott JP, et al. Long-term hydroxyurea therapy for infants with sickle cell anemia: The HUSOFT extension study. Blood. 2005;106(7):2269–75.

[58] Kinney TR, Helms RW, Branski EEO, Ohene-frempong K, Wang W, Daeschner C, et al. Safety of hydroxyurea in children with sickle cell anemia: Results of the HUG-KIDS study, a phase I/II trial. 1999;1550–4.

[59] Ohene-Frempong K, Weiner SJ, Sleeper L a, Miller ST, Embury S, Moohr JW, et al. Cerebrovascular accidents in sickle cell disease: Rates and risk factors. Blood [Internet]. 1998;91(1):288–94. Available from: http://www.ncbi.nlm.nih.gov/pubmed/9414296

[60] Nichols FT, Jones AM, Adams RJ. Stroke prevention in sickle cell disease (STOP) study guidelines for transcranial Doppler testing. J Neuroimaging [Internet]. 2001 [cited 2013 Feb 19];11(4):354–62. Available from: http://www.ncbi.nlm.nih.gov/pubmed/11677874

[61] Adams R, McKie V, Nichols F. The use of transcranial ultrasonography to predict stroke in sickle cell disease. N Engl J Med [Internet]. 1992 [cited 2013 Feb 10]; Available from: http://www.nejm.org/doi/full/10.1056/NEJM199202273260905

[62] Adams RJ. Big strokes in small persons. Arch Neurol [Internet]. 2007;64(11):1567–74. Available from: http://www.ncbi.nlm.nih.gov/pubmed/17998439

[63] DeBaun MR, Gordon M, McKinstry RC, Noetzel MJ, White DA, Sarnaik SA, et al. Controlled trial of transfusions for silent cerebral infarcts in sickle cell anemia. N Engl J Med [Internet]. 2014;371(8):699–710. Available from: http://www.ncbi.nlm.nih.gov/pubmed/25140956

[64] DeBaun MR, Armstrong FD, McKinstry RC, Ware RE, Vichinsky E, Kirkham FJ. Silent cerebral infarcts: A review on a prevalent and progressive cause of neurologic injury in sickle cell anemia. Blood [Internet]. 2012 [cited 2012 Nov 3];119(20):4587–96. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22354000

[65] Gladwin MT, Ghofrani H. Pulmonary and critical care updates. Update on pulmonary hypertension. 2009;(6).

[66] Ansong D, Akoto AO, Ocloo D, Ohene-frempong K. Sickle cell disease: Management options and challenges in developing countries. 2013.

[67] Kato GJ, McGowan V, Machado RF, Little JA, Taylor J, Morris CR, et al. Lactate dehydrogenase as a biomarker of hemolysis-associated nitric oxide resistance, priapism, leg ulceration, pulmonary hypertension, and death in patients with sickle cell disease. Blood [Internet]. 2006 [cited 2012 Nov 24];107(6):2279–85. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=1895723&tool=pmcentrez&rendertype=abstract

[68] Kato GJ, Hsieh M, Machado R, Vi JT, Little J, Butman JA, et al. NIH Public Access. 2008;81(7):503–10.

[69] Sebastiani P, Nolan VG, Baldwin CT, Abad-grau MM, Wang L, Adewoye AH, et al. Red cells a network model to predict the risk of death in sickle cell disease. Cell. 2007;110(7):2727–35.

[70] Menzel S, Rooks H, Zelenika D, Mtatiro SN, Gnanakulasekaran A, Drasar E, et al. Global genetic architecture of an erythroid quantitative trait locus, HMIP-2. Ann Hum Genet. 2014;434–51.

[71] Mtatiro SN, Makani J, Mmbando B, Thein SL, Menzel S, Cox SE. Genetic variants at HbF-modifier loci moderate anemia and leukocytosis in sickle cell disease in Tanzania. Am J Hematol [Internet]. 2015;90(1):E1–4. Available from: http://doi.wiley.com/10.1002/ajh.23859

[72] National Heart Lung and Blood Institute. Evidence-based management of sickle cell disease: Expert Panel Report (EPR). Guidel Expert Panel Rep. 2014.