Major clinical aspects of sickle cell anemia, challenges in management

Naif Jazaa Al Johani, Maram Sultan Althagafi, Fayeza Emadaldeen Alam, Mohammed Mostfa Barnawi, Eyad Mosleh Alnajrani

Abstract:

Sickle cell disease (SCD) is one of the most common genetic diseases worldwide. We briefly review the currently available treatments for SCD and diagnosis methods in clinics. We conducted a search of the Cochrane database to evaluate the of sickle cell anemia, challenges in management that were studied up to 2017. We used this list as MeSH terms or equivalent to compose searches of MEDLINE and EMBASE. We also included *chronic lung disease* as a title and abstract search term. Newborn testing, early preventative therapies, education about difficulties, and testing programs enhance both the morbidity and mortality of SCA. In general, the proof suggests that SCT might be neither an entirely benign carrier state nor a true disease entity, but instead a danger aspect for sure adverse results that result from the interplay in between hereditary and environmental influences. VTE and renal condition are among the manifestations under reevaluation. Currently, the results from case-control research studies stay suggestive of an association with these results yet have to be regarded as being far from definitive. Until such time as these observations have been verified, expanding screening efforts have to be considered to be of little advantage. Nonetheless, with continuous newborn testing identifying people with SCT, furthering research to better identify the consequences of SCT is of critical significance to providing much better counseling on any type of involved health risks. Much more hostile treatment of SCA is supported by present evidence, and restorative alternatives with hydroxyurea need to be taken into consideration early in life.

Introduction:

Homozygous sickle cell disease (SCD) is an autosomal recessive genetic disease that results from the alternative of valine for glutamic acid at position 6 of the β-globin gene, resulting in manufacturing of a faulty form of hemoglobin, hemoglobin S (HbS). The prevalence of SCD has to do with 1-- 2% amongst African descendants in Europe and the United States and 4% or higher in West Africa. SCD shows broad phenotypic expression that varies greatly between regions, amongst patients and longitudinally in the same patient [1], [2].The protean clinical features of SCD result from chronic variable intravascular hemolysis, microvascular ischemia and organ damage. Vaso-occlusion is the result of a dynamic mix of abnormalities in hemoglobin framework and function, red blood cell membrane integrity, erythrocyte density, endothelial activation, microvascular tone, inflammatory mediators, and coagulation. These pathophysiologic occasions translate right into clinical manifestations that fall into four general classifications: anemia and its sequelae; vaso-occlusive crises and bone marrow fat embolization disorder; infection (from functional asplenia) and body organ disorder. Body organ damages results from a combination of hemolysis and infarction and could be manifested as stroke, retinopathy, nephropathy, liver disease or pulmonary arterial hypertension. Intravascular hemolysis in SCD triggers the release of hemoglobin right into the plasma. When the ability of protective hemoglobin-scavenging mechanisms (haptoglobin and hemopexin) has been filled, degrees of cell-free hemoglobin increase in the plasma resulting in the intake of nitric oxide (NO) by hemoglobin-mediated NO scavenging [3].Furthermore, arginase launched by hemolyzed red cells can deplete blood plasma of arginine, the substrate for NO production by NO synthase [4].NO plays a major function in vascular homeostasis and is a crucial regulator of smooth muscular tissue leisure and vasomotor tone,

expression of endothelial attachment particles and platelet activation and gathering [5].A shortage in NO, as a result of its inactivation by cell-free plasma hemoglobin degrees during intravascular hemolysis in SCD, might underlie difficulties related to SCD [6].

Sickle cell disease (SCD) is one of the most common genetic diseases worldwide. We briefly review the currently available treatments for SCD and diagnosis methods in clinics.

Methodology:

We conducted a search of the Cochrane database to evaluate the of sickle cell anemia, challenges in management that were studied up to 2017. We used this list as MeSH terms or equivalent to compose searches of MEDLINE and EMBASE. We also included *chronic lung disease* as a title and abstract search term. We included search terms: *of sickle cell anemia, management*. We performed an additional search to identify related references to our studies among the reviewed articles.

Discussion:

Diagnosis

The hallmark testing method for SCD and it variations is Hbelectrophoresis; an electrical area applied to a gel matrix is utilized to divide the various kinds of hemoglobin. A qualitative and quantitative analysis is then done to determine if there is regular Hemoglobin A or one of the defective hemoglobinopathies. A current blood transfusion could obscure the accuracy of the examination.

The scientific research behind laboratory diagnosis of sickle cell condition entails phenotypic testing for the presence the sickle haemoglobin and genetic analysis. Physicochemical properties of the sickle haemoglobin such as lowered solubility and sickling under deoxy conditions, its pattern of mobility in an electric area, and rate of elution from service unto adsorbents are applied in its laboratory discovery. Phenotypic tests might be used as screening examinations or analysis examinations. Screening examinations selected for the function of mass testing need to be highly delicate and cheap to run. Instances of screening tests consist of sickling test, solubility test, and alkaline haemoglobin electrophoresis. On the other hand, high specific, diagnostic examinations include isoelectric concentrating, citrate agar electrophoresis, and high performance liquid chromatography [7].Quantification of haemoglobin versions and globin chain research studies are applied in assessment of substance heterozygous condition states such as sickle thalassemia syndrome [9] Hb A2 levels over of 3.5% are suggestive of haemoglobin S-beta thalassemia [8].Other supplementary laboratory investigations helpful in detection and monitoring of the disease include FBC, reticulocyte count, and peripheral blood film. Reticulocyte count generally range from 5 to 15% in sickle cell illness. On peripheral blood film assessment, results could consist of irreversible sickled red cells, polychromasia, occasional nucleated red cells, and schistocytes, along with Howell-Jolly bodies [11]. Target cells are seen in sickle haemoglobinopathies. In sickle cell thalassemia disorders, target cells are seen together with microcytes and moderate-severe hypochromia. Red cell indices could recommend macrocytosis due to boosted reticulocytosis or conformity with hydroxyurea therapy. Nevertheless, oblong macrocytosis with hypersegmented neutrophils might recommend folic acid deficiency. Biochemical adjustments include high LDH, low haptoglobin, high total and indirect bilirubin, and high AST. Genetic research studies such as PCR are used for prenatal and preimplantation diagnosis [10].

- **Therapeutic effects**

Urgent erythrocyte transfusions are suggested for several acute difficulties of SCA including ACS, ASSC, short-term aplastic dilemma owing to parvovirus B19 infection, and acute stroke. In these settings, transfused blood aids to reduce anemia, improve distributing blood quantity, rise oxygen-carrying ability, and provide erythrocytes that could not sickle. If the posttransfusion target is high sufficient, transfusions likewise assist suppress endogenous sickle erythropoiesis. Optional transfusions are commonly given for preoperative management, to avoid perioperative sickle-related difficulties. Chronic transfusions given on a monthly basis are additionally extremely efficacious for primary and additional stroke avoidance. On the other hand, transfusions are not indicated for acute unpleasant events or anemia in itself (recognizing that nearly all patients have a standard steady-state partly compensated hemolytic anemia), and have little duty in the management of standard VOE [12].

In most acute settings, easy transfusions with packed erythrocytes (PRBC) need to be provided. PRBC are readily offered across the United States, and are consistently evaluated for HIV in addition to liver disease B and C. As a general principle, simple transfusions ought to be given with a target of relieving anemia or dealing with the underlying condition; entire devices (or half devices for little pediatric patients) need to be provided whenever feasible, rather than fixed volumes (e.g., 10 mL/kg), in order to help limit foreign antigen exposure. The posttransfusion target hemoglobin concentration ought to not exceed 10- 11 g/dL in the neglected patient since hyperviscosity could take place; in chronically transfused patients with low %HbS, nonetheless, the posttransfusion target can be increased in order to help suppress endogenous erythrocyte manufacturing. It is likewise essential for the Blood Bank to be mindful that the patient has SCA, because extending

red blood cell (RBC) phenotype matching for minor blood group antigens is advised to assist avoid alloimmunization [13].

For patients with neurological signs for chronic transfusion therapy such as abnormal TCD speeds or stroke, duplicated simple transfusions work in avoiding primary and secondary stroke, respectively, but inevitably cause transfusional iron overload. For this reason, partial exchange transfusions or isovolemic erythrocytapheresis is advised to minimize iron accumulation. In most patients, intravenous access for exchange transfusions is facilitated by the placement of an implantable device. With chronic transfusions, the objective is usually HbS $\leq$ 30% as a pretransfusion worth, which generally needs transfusion every 3- 5 weeks depending on the type and quantity of each transfusion, the patient's own erythropoietic drive, and the response to transfusion treatment. Chelation treatment for transfusional iron overload should be considered for all patients on chronic transfusions, however also for teens and adults that have a big advancing number of episodic or sporadic transfusions.

- **Hydroxyurea**

Increased fetal hemoglobin (HbF) levels have been associated with a much less severe phenotype of SCA [15] and HbF induction has ended up being a desired pharmacologic end point for SCA therapy [14].Hydroxyurea has been shown to potently raise HbF and is currently the most reliable disease-modifying therapy for both adults and children with SCA [17].The very first clinical experience with hydroxyurea for SCA was reported almost 30 years back in seminal proof-of-principles studies [17].Consequently, a multicenter phase II research study recorded laboratory efficacy (boosted Hb, %HbF, and MCV; reduced WBC, ANC, ARC, and platelets) of hydroxyurea using a dose escalation schedule to MTD [14].The Multi-Center Study of Hydroxyurea (MSH) double-blinded, placebo-controlled randomized medical trial revealed medical efficacy of

hydroxyurea for adults with extreme SCA, with substantially reduced time to initially unpleasant event, plus less episodes of ACS, transfusions, and hospital stays [16].

In children with SCA, similar laboratory and medical efficiency have been displayed in open-label tests [18], [19].In hydroxyurea research study of long-lasting effects (HUSTLE), all pediatric patients with medication adherence had HbF responses, although reactions varied and potentially related to differences in medicine absorption, pharmacokinetics, and pharmacogenetics [20].The results from the double-blinded, placebo-controlled multicenter randomized BABY HUG study reveal the security and medical efficiency of hydroxyurea for young infants with SCA, regardless of previous scientific severity [19].The primary end point of BABY HUG was the ability of hydroxyurea to avoid chronic organ damage (kidney, spleen), and the short-term research study results were equivocal. Anecdotal records recommend prevention and even reversal of chronic organ damage with hydroxyurea treatment [21], so additional investigation of the BABY HUG cohort is essential.

Long-term follow up from MSH and the Greek Laikon Study of Hydroxyurea in Sickle Cell Syndromes recorded reduced death for grown-up patients with SCA on hydroxyurea [22]. There is currently indisputable evidence that hydroxyurea has laboratory and clinical efficiency for any ages; a growing body of evidence also supports the long-lasting safety of hydroxyurea and the ability of hydroxyurea to avoid chronic organ damage and reduce death [23].Whereas hydroxyurea formerly has been booked for older patients with an extreme clinical course, hydroxyurea use should be liberalized and provided to all grownups with SCA. An increasing number of pediatric hematologists believe hydroxyurea should currently be taken into consideration as a treatment alternative for all kids with SCA, no matter age or previous medical program.

Hydroxyurea should be started by a knowledgeable clinician aware of laboratory surveillance and proper dosage escalation to MTD. Hydroxyurea treatment must commence at ~ 20 mg/kg/d by mouth, once daily. Complete blood count (CBC) must be checked every 4 wk to monitor for myelosuppression, which is usually mild and dosage dependent, and always reversible by holding the hydroxyurea dosage temporarily [24].Dosage competence and medication compliance can be examined by examining adjustments in CBC criteria and reviewing the outer blood smear. To get to MTD, the everyday dosage ought to be intensified by ~ 5 mg/kg every 8 wk till MTD is moderate neutropenia (e.g., ANC of 1500-- 3000 × 106/L) or reticulocytopenia (ARC of 100- 150 × 109/L) is reached on a secure dosage. Medication toxicity is generally defined by cytopenias such as ANC <1.0 × 109/L, hemoglobin <7.0 g/dL with low reticulocyte matter, ARC <80 × 109/L, and platelets <80 × 109/L [24].Given the unlikelihood of real hydroxyurea "nonresponders," efforts need to be made to urge medication conformity to reach and preserve a stable and effective hydroxyurea MTD [25].

- **Other treatmens**

HbF induction can be achieved by a group of short-chain fats that prevent the enzyme histone deacetylase; such HDAC preventions, primarily butyrate, can change chromatin framework and induce HbF production by modifying the transcription of the γ-globin gene [26].Scientific experience with HDAC inhibitors for SCA is limited however anecdotal reports suggest durable HbF induction in some patients with SCA [27].

Decitabine is a nucleoside analog that generates HbF induction by means of epigenetic modulation, especially hypomethylation of the γ-globin genetics marketer. Experience with decitabine for SCA is additionally relatively minimal, however a number of reports suggest clinical and laboratory efficiency of subcutaneously provided decitabine in grownups who were not responsive to

hydroxyurea [28].Possible trials of decitabine are necessitated to determine if it has efficacy for a broad spectrum of patients with SCA.

Added therapies that target certain pathways of the pathophysiology of SCA are just participating in professional trials. One new appealing inhibitor of the Gardos channel was discovered to have favorable impacts on hemolysis and RBC survival, yet did not have professional efficacy in a stage III randomized clinical trial [29].

Conclusion:

Sickle cell disease can have a damaging impact on the lifestyle and greatly reduce life span in sufferers. Decades of observational studies and therapeutic tests have resulted in a higher understanding of the pathophysiology and management of SCA. Based upon these outcomes, relatively simple interventions can considerably improve the survival of SCA, especially among children. Newborn testing, early preventative therapies, education about difficulties, and testing programs enhance both the morbidity and mortality of SCA.

In general, the proof suggests that SCT might be neither an entirely benign carrier state nor a true disease entity, but instead a danger aspect for sure adverse results that result from the interplay in between hereditary and environmental influences. VTE and renal condition are among the manifestations under reevaluation. Currently, the results from case-control research studies stay suggestive of an association with these results yet have to be regarded as being far from definitive. Until such time as these observations have been verified, expanding screening efforts have to be considered to be of little advantage. Nonetheless, with continuous newborn testing identifying people with SCT, furthering research to better identify the consequences of SCT is of critical significance to providing much better counseling on any type of involved health risks. Much more

hostile treatment of SCA is supported by present evidence, and restorative alternatives with hydroxyurea need to be taken into consideration early in life.

Reference:

1. Stuart MJ, Nagel RL. Sickle-cell disease. Lancet. 2004;364:1343–60.
2. Schnog JB, Duits AJ, Muskiet FA, ten Cate H, Rojer RA, Brandjes DP. Sickle cell disease; a general overview. Neth J Med. 2004;62:364–74.
3. Rother RP, Bell L, Hillmen P, Gladwin MT. The clinical sequelae of intravascular hemolysis and extracellular plasma hemoglobin: a novel mechanism of human disease. JAMA. 2005;293:1653–62.
4. Morris CR, Kato GJ, Poljakovic M, Wang X, Blackwelder WC, Sachdev V, et al. Dysregulated arginine metabolism, hemolysis-associated pulmonary hypertension and mortality in sickle cell disease. JAMA. 2005;294:81–90.
5. Walford G, Loscalzo J. Nitric oxide in vascular biology. J Thromb Haemost. 2003;1:2112–8.
6. Lin EE, Rodgers GP, Gladwin MT. Hemolytic anemia-associated pulmonary hypertension in sickle cell disease. Curr Hematol Rep. 2005;4:117–25.
7. Kotila T. R. Guidelines for the diagnosis of the haemoglobinopathies in Nigeria. Annals *of* Ibadan Postgraduate Medicine. 2011;8(1):25–29. doi: 10.4314/aipm.v8i1.63954.
8. Daniel Y. Haemoglobinopathy diagnostic tests: blood counts, sickle solubility test, haemoglobin electrophoresis and high-performance liquid chromatography. In: Okpala I. E., editor. Practical Management of Haemoglobinopathies. Blackwell Publishing; 2004. pp. 10–19.
9. Bain B. J. Haemoglobinopathy diagnosis: algorithms, lessons and pitfalls. *Blood Reviews*. 2011;25(5):205–213. doi: 10.1016/j.blre.2011.04.001.
10. Clarke G. M., Higgins T. N. Laboratory investigation of hemoglobinopathies and thalassemias: review and update. Clinical Chemistry. 2000;46(8, part 2):1284–1290.
11. Rahim F. The sickle cell disease. Haematology Updates, 2010.
12. Smith-Whitley K, Thompson AA 2012. Indications and complications of transfusions in sickle cell disease. Pediatr Blood Cancer 59: 358–364.
13. Yazdanbakhsh K, Ware RE, Noizat-Pirenne F 2012. Red blood cell alloimmunization in sickle cell disease: Pathophysiology, risk factors, and transfusion management. Blood 120: 528–537.
14. Charache S, Terrin ML, Moore RD, Dover GJ, Barton FB, Eckert SV, McMahon RP, Bonds DR, and the Investigators of the Multicenter Study of Hydroxyurea in Sickle Cell Anemia 1995. Effect of hydroxyurea on the frequency of painful crises in sickle cell anemia. N Engl J Med 332: 1317–1322.
15. Conley CL, Weatherall DJ, Richardson SN, Shepard MK, Charache S 1963. Hereditary persistence of fetal hemoglobin: A study of 79 affected persons in 15 Negro families in Baltimore. Blood 21: 261–281.

16. Charache S, Dover GJ, Moore RD, Eckert S, Ballas SK, Koshy M, Milner PF, Orringer EP, Phillips G Jr, Platt OS 1992. Hydroxyurea: Effects on hemoglobin F production in patients with sickle cell anemia. Blood 79: 2555–2565.
17. Platt OS, Orkin SH, Dover G, Beardsley GP, Miller B, Nathan DG 1984. Hydroxyurea enhances fetal hemoglobin production in sickle cell anemia. J Clin Invest 74: 652–656.
18. Kinney TR, Helms RW, O'Branski EE, Ohene-Frempong K, Wang W, Daeschner C, Vichinsky E, Redding-Lallinger R, Gee B, Platt OS, et al. 1999. Safety of hydroxyurea in children with sickle cell anemia: Results of the HUG-KIDS study, a phase I/II trial. Pediatric Hydroxyurea Group. Blood 94: 1550–1554.
19. Wang WC, Ware RE, Miller ST, Iyer RV, Casella JF, Minniti CP, Rana S, Thornburg CD, Rogers ZR, Kalpatthi RV, et al. 2011. Hydroxycarbamide in very young children with sickle-cell anaemia: A multicentre, randomised, controlled trial (BABY HUG). Lancet 377: 1663–1672.
20. Ware RE, Despotovic JM, Mortier NA, Flanagan JM, He J, Smeltzer MP, Kimble AC, Aygun B, Wu S, Howard T, et al. 2011. Pharmacokinetics, pharmacodynamics, and pharmacogenetics of hydroxyurea treatment for children with sickle cell anemia. Blood 118: 4985–4991.
21. Zimmerman SA, Schultz WH, Burgett S, Mortier NA, Ware RE 2007. Hydroxyurea therapy lowers transcranial Doppler flow velocities in children with sickle cell anemia. Blood 110: 1043–1047.
22. Steinberg MH, McCarthy WF, Castro O, Ballas SK, Armstrong FD, Smith W, Ataga K, Swerdlow P, Kutlar A, DeCastro L, et al. 2010. The risks and benefits of long-term use of hydroxyurea in sickle cell anemia: A 17.5 year follow-up. Am J Hematol 85: 403–408.
23. McGann PT, Ware RE 2011. Hydroxyurea for sickle cell anemia: What have we learned and what questions still remain? Curr Opinion Hematol 18: 158–165.
24. Heeney MM, Ware RE 2008. Hydroxyurea for children with sickle cell disease. Pediatr Clin N Am 55: 483–501.
25. Ware RE 2010b. How I use hydroxyurea to treat young patients with sickle cell anemia. Blood 115: 5300–5311.
26. McCaffrey PG, Newsome DA, Fibach E, Yoshida M, Su MS 1997. Induction of γ-globin by histone decetylase inhibitors. Blood 90: 2075–2083.
27. Atweh GF, Sutton M, Nassif I, Boosalis V, Dover GJ, Wallenstein S, Wright E, McMahon L, Stamatoyannopoulos G, Faller DV, et al. 1999. Sustained induction of fetal hemoglobin by pulse butyrate therapy in sickle cell disease. Blood 93: 1790–1797 .
28. Creusot F, Acs G, Christman JK 1982. Inhibition of DNA methyltransferase and induction of Friend erythroleukemia cell differentiation by 5-azacytidine and 5-aza2′-deoxycytidine. J Biol Chem 257: 2041–2048
29. Ataga KI, Reid M, Ballas SK, Yasin Z, Bigelow C, James LS, Smith WR, Galaceros F, Kutlar A, Hull JH, et al. 2011. Improvements in haemolysis and indicators of erythrocyte survival do not correlate with acute vaso-occlusive crises in patients with sickle cell disease: A phase III randomized placebo-controlled double-blind study of the Gardos channel blocker senicapoc (ICA-17043). Br J Hematol153: 92–104