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Egyptian perspective of research in sickle cell disease

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Abstract

Objective: Hemoglobinopathies including sickle cell disease (SCD) are prevalent inherited disorders in most Arab countries including Egypt. The heterogeneous distribution with variable prevalence in Egypt may be due to the historical trade exchange, high prevalence of consanguineous marriage, and internal migration.

Materials and methods: The literature search was conducted in the PubMed MEDLINE database including articles indexed as of 15th Apr 2024, if they involved patients with SCD in Egypt.

Results: In this work, we presented the research originated from Egypt addressing the SCD which includes case reports, original articles, and randomized clinical trials, and highlighted how this research efforts open the doors for understanding the prevalence and pathophysiology, improvement of the diagnostic methods, and the breakthrough treatment.

Conclusions: Although scanty research was carried out in the nineteenth century and the first decade of the twentieth century, SCD became an area of focus for research in 2010. The standard of care and the infrastructure improved with the involvement of several centres in multicenter international clinical trials.

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Introduction

Sickle cell disease (SCD) is one of the most common monogenic disorders that arise from a missense mutation in the β-globin gene (HBB) (1). For hundreds of years, even before documenting the first known case of SCD in the United States (2), intermarriages have occurred among inhabitants of the equatorial border of Egypt and those of the neighbouring Sub-Saharan Africa (SSA) countries. In its western desert near the Libyan border variable rates of 0.38 % in the coastal areas to 9.0 % in the New Valley oases have been reported (3).

There is no precise global data regarding the number of children born with SCD because newborn screening for SCD is not available in most resource-poor countries with the highest predicted burdens, based on carrier frequencies and global birth rates, it was estimated that around 312,000 children are born each year with sickle cell anaemia (HbSS). There is more limited data on allele frequency for HbC and β-thalassemia, so it is more difficult to estimate the numbers born with other forms of SCD, which is probably a further 50,000–100,000 births per year (4).

The goals of the treatment of SCD are symptom control with early detection and management of disease complications (5). Clinical research has an important role in enhancing children's health, as many treatment options used today were previously tested in randomized clinical trials (RCTS) which help us understand, prevent, and treat SCD. The American Society of Hematology Research Collaborative (ASH RC) has created the Sickle Cell Disease Clinical Trials Network to offer resources to educate patients and expand the range of safe and effective treatment options (6). The DOVE (Determining Effects of Platelet Inhibition on Vaso-Occlusive Events) study highlighted the importance of ensuring diversity, as the disease phenotype and adverse event may differ due to cultural diversities, resource utilization or disease severity, these data help in planning future trials in SCA in a multinational setting (7).

Materials and methods

In this work, we presented the importance of the research to understand the prevalence and pathophysiology, improve the diagnostic methods and the breakthrough treatment, and highlight how Egypt contributed to this success. The literature search was conducted in the PubMed MEDLINE database which included articles indexed as of 15th Apr 2024, without publication date restriction. Studies were included if they (1) involved patients with SCD (HbSS, HbSC, HbS/β0/+ thalassemia); (2) If the studied populations included Egyptian patients or were conducted in Egypt. The search terms combined (1) Sickle AND (2) Egypt and the literature search identified 262 articles.

Results

The flow diagram detailing the selection of studies included in this article categorized by the time of publication is provided in **Figure 1**. Three categories were defined as follows:

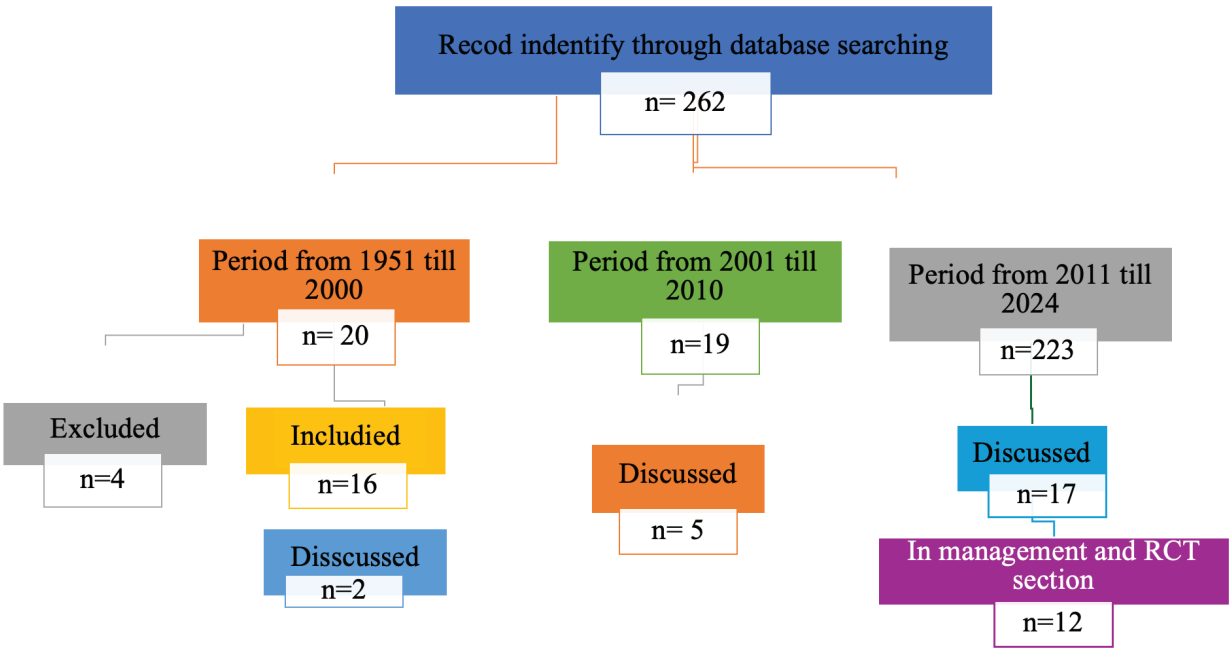

Figure 1: The flow diagram detailing the selection of studies included in this article when categorized by the time of publication

A. From 1951 till 2000: Since the first reported case in Egypt was in 1951 (8) till 2000 only individualized research with few national or institutional works published regarding SCD, mainly few case reports and papers. Two research papers published over this period have recruited a reasonable number of subjects and will be discussed (9,10).

B. 2001 till 2010: The literature search identified 19 articles; two were excluded including one that was not related to SCD, and the other did not involve a population from Egypt. Of the included seventeen, four will be discussed; one regarding prevalence and prevention (11), and one of the three records that related to the death of the Egyptian king (12-14) will be discussed in the prevalence section, two represent the first single site RCTs in Egypt (15,16) as well as the first RCT (EPIC) study (17) that will be discussed in the RCT and management section.

C. 2011 till 2024: The literature search identified 223 articles, of which 17 articles were discussed mainly in the management and RCT section (n=12)

The detailed selection of studies (n=262) included in this article when categorized by type were mainly full text (n=233, 88.9%), clinical trial (n=25, 9.6%), review of article (n=20, 7.6%), systematic review (n=4, 1.5%), and none presented as book/documents.

The four systematic reviews discussed SCD in general not specifically for Egypt; one review was about rare genotypes including 68 HbSE patients reported in the literature (18), another was a critical appraisal of the quality of recent clinical practice guidelines for managing pregnant women with SCD (19), the third systemic review assesses the clinical benefits and harms of antiplatelet agents in patients with SCD including RCTs (20), and the fourth was an article

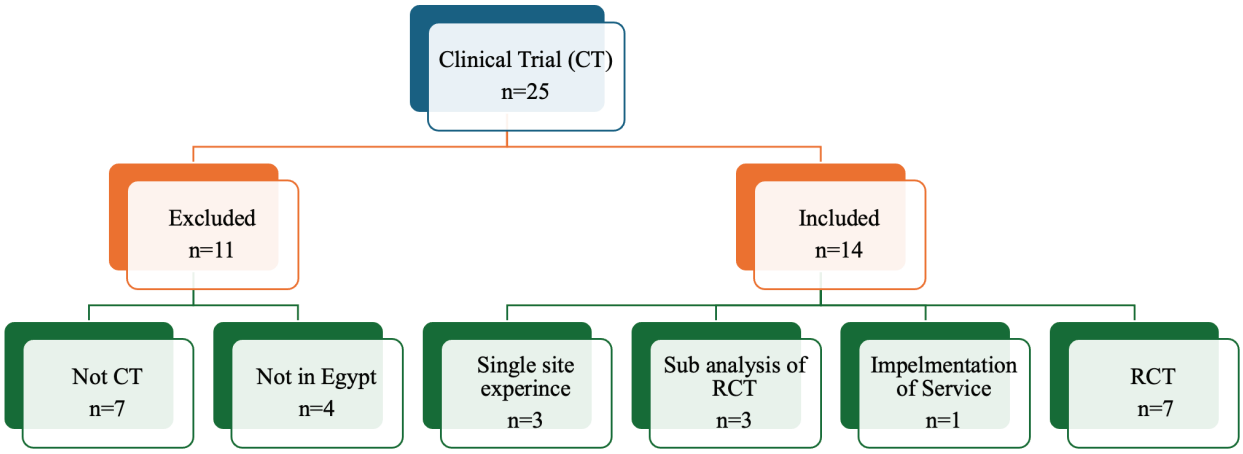

Figure 2: The flow diagram detailing the selection of clinical trials included in this article

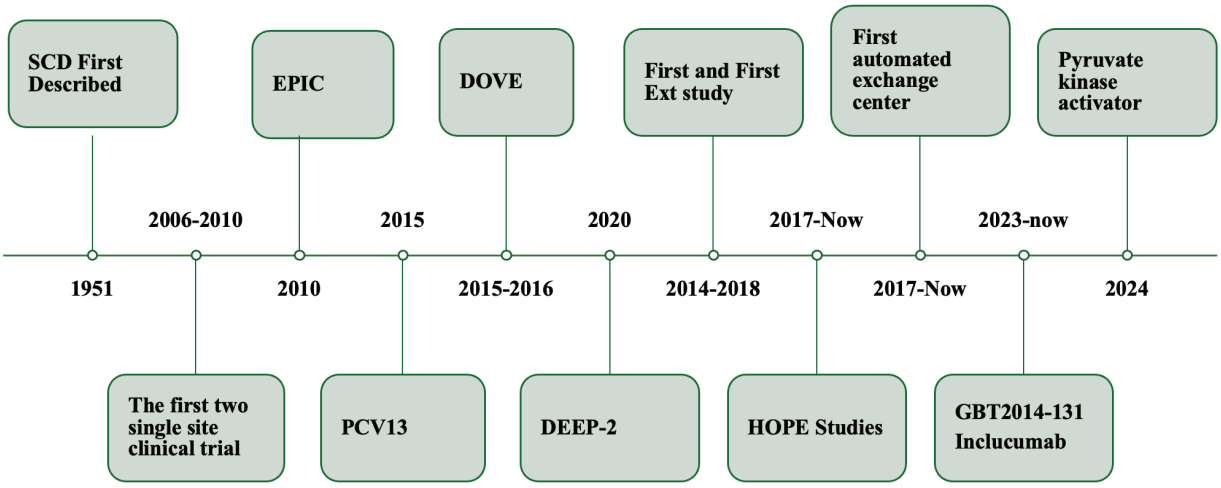

Figure 3: Flow diagram detailing the significant milestones in the research in Egypt

that systematically evaluated the different types of technological tools used for self-management of SCD and assessed its efficacy (21).

Up to our database searches, twenty-five studies were categorized as clinical trials, the flow diagram detailing the selection of studies included in this article is provided in **Figure 2**. Eleven records were excluded; 7 were not RCT and 4 were not in Egypt, while 14 included 3 were single experience, 3 sub-analyses of RCT, one was an implementation of service and seven RCT. One of the first international RCT to include SCD in Egypt (EPIC study) did not appear in the search engine as RCT (17). The timeline of the history of SCD in Egypt, from discovery over past years to the current treatment landscape, explores the significant milestones illustrated in **Figure 3**.

Discussion

The breakthrough in understanding SCD hit when Pauling's research for haemoglobin (Hb) using the electrophoresis technique discovered that SCD results from a change in protein structure and became the first molecular disease to be discovered (22). Unfortunately, in the initial progress in understanding the pathophysiology and diagnosis of SCD, no research was published from Egypt as the first case diagnosed was in 1951 (8), this was followed by publishing a few case reports and papers (23-31). Salah et al., 1991 studied the significant factors that may contribute to complications in 100 pregnant mothers with SCD (35 HbSS and 65 sickle cell trait (HbAS)) and concluded high levels of fetal Hb did not have any beneficial effect in patients with SCD during VOCs (9). el-Hazmi et al., 1999 performed collaborative research on patients with SCD from Egypt, the Syrian Arab Republic, Jordan, and Saudi Arabia, they suggest that HBB gene haplotypes influence the clinical presentation of SCD and that there are at least two major foci for the origin of the sickle-cell gene, one in the eastern part of Saudi Arabia, and the other in the populations of North Africa and the north-western part of the Arabian Peninsula (10).

From 2000 till 2010; few academic papers were published focusing mainly on the prevalence. Of interest, a work raised the hypothesis that SCA or $HbS\beta_0$ is the cause of death for Tutankhamun instead of Freiberg-Kohler syndrome has been published (14). A work investigating the distribution of SCD confirmed that it is not frequent in Egypt except in the Oases where the carrier rate varies from 9 to 22% (11). Another study screened 349 primary school children in the closed isolated community of Siwa Oasis for abnormal Hb profiles, 22% had abnormal Hb profiles, of whom 88% had HbS (94% of them SA and 6% are SS) (32). Another study estimated the rate of sickle cell trait in Arab countries is 0.3- 30 %, with the Arab Indian associated with mild phenotype and the Benin and Bantu associated with severe phenotype constituting the bulk of the haplotypes (33), while a WHO report estimated that the carrier frequency is 1–2% on the North African coast (34). The strong cultural preferences for consanguineous marriage and limited preventive programs and resources have harmed the management of Egyptian thalassemic patients (35), the public health approaches targeting the prevention of hemoglobinopathies are still patchy and inadequate in many Arab countries recommending the upgrade of these services and raising public awareness (33).

Focusing on SCD management, since the beginning of the 2010 century, SCD has started to gain the scientific attention of the academic society, with around two hundred works published, facilitating the inclusion of Egypt in interventional clinical trials. Hydroxyurea (HU) the first approved drug to treat SCD was studied in a retrospective Egyptian study to evaluate its long-term effects on Hb, showed that it induced an increase in Hb F level, which was maintained over time and was associated with clinical efficacy and acceptable safety in SCD patients (36). Another recent cross-section Egyptian study determine the frequency of sleep-disordered breathing in children with SCD showed that nearly all patients (29 out of 30) were receiving HU as the standard of care (37). Owing to the importance of transfusion of red blood cells (RBCs) in SCD management, a prospective, investigator-initiated non-randomized open-label interventional, single Egyptian centre study (NCT03903289) describes the implementation of the first automated erythrocytapheresis centre in Egypt in 2017 to improve the standard of care demonstrated that automated erythrocytapheresis is a safe and effective modality for the management of patients with SCD (38).

Iron chelation is required to prevent iron overload with one of the three iron chelators (deferiprone, deferasirox, or deferoxamine). Of note, one of the investigator-initiated evaluated the safety and efficacy of a new liquid formulation of deferiprone for the treatment of 100 transfusional iron overload in children

1-10 years old (16) and although it includes only one child with SCD, it opens the door for the following RCTs. The FIRST (Ferriprox in Patients With Iron Overload in Sickle Cell Disease Trial), a one-year randomized noninferiority study (NCT02041299) in patients with SCD receiving chronic transfusion therapy including a total of 228 patients, a large number of them were from Egypt demonstrated the noninferiority of deferiprone in managing iron overload and safe profiles (39). A post hoc analysis of the FIRST study included patients 17 years and younger with SCD confirmed previous findings in adults that deferiprone is comparable to deferoxamine in reducing iron overload and showed that it could improve adherence and outcomes in children (40). The same findings were found from the long-term FIRST EXT (NCT02443545), a 2-year extension study of the FIRST study (41). The deferasirox was tested in The multicenter Evaluation of Patients' Iron Chelation with Exjade (EPIC) study, which enrolled 1744 among them 80 had SCD and demonstrated that it could provide effective chelation as assessed by a decline in serum ferritin (17). Data were collected before and after 1 year of deferasirox treatment from EPIC to evaluate trends between liver iron concentration (LIC), transferrin saturation (TfSat), pre-dose labile plasma iron (LPI), and their relationship to SF categories demonstrated that despite limitations, SF showed that the clearest relationship of markers evaluated to LIC (NCT00171821). (42) The DEEP-2 study (NCT01825512) which was a phase 3, multicenter, randomized trial in pediatric patients with transfusion-dependent hemoglobinopathies in 21 research hospitals and universities including Egypt established a non-inferiority of deferiprone versus deferasirox with treatment success in 69 (55·2%) of 125 patients assigned deferiprone vs 80 (54·8%) of 146 assigned deferasirox (43).

Bone marrow transplant (BMT) as a treatment modality faces many obstacles that limit its use in Egypt as the lack of resources, the lack of fully matched sibling donors and concerns about transplant-related toxicities. A retrospective analysis of the Eastern Mediterranean Blood and Marrow Transplantation (EMBMT) group studied the trends of HSCT activities in the World Health Organization-Eastern Mediterranean (EMRO) region, between 2011 and 2012, showed that hemoglobinopathies, particularly thalassemia representing around 11% only (44).

The second approved drug for SCD management, l-glutamine, was tested in a single-site RCT to investigate the gaps in its therapeutic implications, especially in LMICs and financial cost compared with HU. The study recruited sixty SCD and found that glutamine reduced the number of VOCs and severity and may have a potentially favourable impact on the cerebral arterial flow velocities (45). The voxelotor, the anti-HbS polymerization drug, was tested in the HOPE (NCT03036813) study that was performed at 60 clinical sites including Egypt, recruited 274 SCD and showed that it significantly increased Hb levels and reduced markers of hemolysis (46) and it (1500 mg) was approved in the USA in SCD patients aged 12 years and older (47). On 24 Sep 2024, Pfizer discontinued all active voxelotor clinical trials and expanded access programs worldwide including Egypt based on the totality of clinical data that indicates the overall benefit no longer outweighs the risk in the approved SCD patient population (48).

The antiplatelet prasugrel was investigated in the Dove (Determining Effects of Platelet Inhibition on Vaso-Occlusive Events) trial (NCT01794000) which included 341 children and adolescents with SCD at 51 sites in 13 countries across the Americas, Europe, Asia, and Africa. It was concluded that the rate of VOCs was not significantly lower among those who received prasugrel than among those who received a placebo (49). Sub-analysis to capture diary completion rates and compliance in children who used the electronic patient-reported outcome diary during the Dove study concluded that with appropriate design, participant training, and sufficient monitoring, an electronic patient-reported outcome diary can capture daily sickle cell-related pain data in large multinational studies (50).

One of the important early RCTs focusing on a vaccine in SCD was addressing the PCV13 vaccine and concluded that children with SCD 6-17 years of age who were previously vaccinated with PPSV23 at least 6 months before study enrollment when they received two doses of PCV13 6 months apart, they responded well to 1 PCV13 dose, and a second dose did not increase antibody response (51). One of the earliest single-site experience examined the clinical manifestations of cardiovascular abnormalities before and after administration of L-carnitine to randomly selected 37 SCD children for 6 months and showed

that cardiac diastolic function and pulmonary hypertension showed some improvement after L-carnitine administration (15). Another single-site RCT enrolled 65 patients randomly assigned to three capsules of either 1,000 mg Omega-3 fish oil or 1.5 mL vitamin D (2,800 IU/7 ml) daily for 10 months plus the standard therapy showed that Omega-3 was more effective than vitamin D or standard treatment alone to relief pain crises (52).

Conclusions

Although scanty research was carried out in the nineteenth century and the first decade of the twentieth century, SCD became an area of focus for research in 2010. The standard of care and the infrastructure improved with the involvement of several Egyptian centers in multicenter international clinical trials paving the way for breakthrough treatment and improved the management.

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Research concept and design: FSEE

Data analysis and interpretation: FSEE

Collection and/or assembly of data: FSEE

Writing the article: FSEE

Critical revision of the article: FSEE

Final approval of the article: FSEE

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References

4. GBD 2021 Sickle Cell Disease Collaborators. Global, regional, and national prevalence and mortality burden of sickle cell disease, 2000-2021: a systematic analysis from the Global Burden of Disease Study 2021. Lancet Haematol. 2023;10(8):e585-e599.

5. Herrick JB, Peculiar elongated and sickle-shaped red blood corpuscles in a case of severe anemia. Arch Internal Med. 1910;6:517–21.

6. El-Hazmi MA, Al-Hazmi AM, Warsy AS. Sickle cell disease in Middle East Arab countries. Indian J Med Res. 2011;134(5):597-610.

7. Chakravorty S, Williams TN Sickle cell disease: a neglected chronic disease of increasing global health importance Archives of Disease in Childhood 2015;100:48-53.

8. Aygun B, Odame IA. global perspective on sickle cell disease. Pediatr Blood Cancer 2012;59(2):386-90.

9. ASH Research Collaborative. https://www.ashresearchcollaborative.org/s/sickle-cell-disease-community. Accessed on 16 March 2024.

10. Inusa BPD, Colombatti R, Rees DC, Heeney MM, Hoppe CC, Ogutu B, et al. Geographic Differences in Phenotype and Treatment of Children with Sickle Cell Anemia from the Multinational DOVE Study. J Clin Med. 2019;8(11):2009.

11. Abbasy AS; Case Report: Sickle Cell Anemia; First Case Reported from Egypt. Blood 1951;6(6):555–8.

12. Salah M, Massoud M, Saleh WA. Effects of maternal sickle cell haemoglobinopathy on pregnancy. J Egypt Public Health Assoc. 1991;66(3-4):373-86.

13. el-Hazmi MA, Warsy AS, Bashir N, Beshlawi A, Hussain IR, Temtamy S, et al. Haplotypes of the beta-globin gene as prognostic factors in sickle-cell disease. East Mediterr Health J. 1999;5(6):1154-8.

14. El-Beshlawy A, Youssry I. Prevention of hemoglobinopathies in Egypt. Hemoglobin. 2009;33:S14-20.

15. Timmann C, Meyer CG. King Tutankhamun's family and demise. JAMA. 2010;303(24):2473; author reply 2473-5.

16. Timmann C, Meyer CG. Malaria, mummies, mutations: Tutankhamun's archaeological autopsy. Trop Med Int Health. 2010;15(11):1278-80.

17. Pays JF. Toutankhamon et sicklanémie (Tutankhamun and sickle-cell anaemia). Bull Soc Pathol Exot. 2010;103(5):346-7.

18. El-Beshlawy A, Abd El Raouf E, Mostafa F, Talaat M, Isma'eel H, Aoun E, et al. Diastolic dysfunction and pulmonary hypertension in sickle cell anemia: is there a role for L-carnitine treatment? Acta Haematol. 2006;115(1-2):91-6.

19. ElAlfy MS, Sari TT, Lee CL, Tricta F, El-Beshlawy A. The safety, tolerability, and efficacy of a liquid formulation of deferiprone in young children with transfusional iron overload. J Pediatr Hematol Oncol. 2010;32(8):601-5.

20. Cappellini MD, Porter J, El-Beshlawy A, Li CK, Seymour JF, Elalfy M, et al. Tailoring iron chelation by iron intake and serum ferritin: the prospective EPIC study of deferasirox in 1744 patients with transfusion-dependent anemias. Haematologica. 2010;95(4):557-66.

21. Khamees I, Ata F, Choudry H, Soliman AT, De Sanctis V, Yassin MA. Manifestations of HbSE sickle cell disease: a systematic review. J Transl Med. 2021;19(1):262.

22. Amer YS, Sabr Y, ElGohary GM, Altaki AM, Khojah OT, El-Malky A, et al. Quality assessment of evidence-based clinical practice guidelines for the management of pregnant women with sickle cell disease using the AGREE II instrument: a systematic review. BMC Pregnancy Childbirth. 2020;20(1):595.

23. Martí-Carvajal A, Abd El Aziz MA, Martí-Amarista C, Solà I. Antiplatelet agents for preventing vaso-occlusive events in people with sickle cell disease: a systematic review. Clin Adv Hematol Oncol. 2019;17(4):234-43.

24. Badawy SM, Cronin RM, Hankins J, Crosby L, DeBaun M, Thompson AA, et al. Patient-Centered eHealth Interventions for Children, Adolescents, and Adults With Sickle Cell Disease: Systematic Review. J Med Internet Res. 2018;20(7):e10940.

25. Pauling L, Itano HA, Singer SJ, Wells IC. Sickle cell anemia a molecular disease. Science. 1949;110(2865):543-8.

26. Ata A EL-H. Sickle cell anaemia; with a case report. J Egypt Med Assoc. 1957;40(11):815-30.

27. Awny AY, Kamel K, Hoerman K. Investigations of hemoglobin variants. 1. Sickle-cell anemia; the importance of a battery of tests for its diagnosis, with a case report. J Egypt Med Assoc. 1960;43:89-95.

28. Rahman AM. Blood dyscrasias and central retinal vein occlusion. Bull Ophthalmol Soc Egypt. 1968;61(65):187-95

29. Kamel K. Hemoglobin variants in U.A.R. J Egypt Public Health Assoc. 1968;43:Suppl:111-7

30. Emarah MH. Ocular manifestations of sickle-cell haemoglobin C disease, report of a case. Bull Ophthalmol Soc Egypt. 1969;62(66):421-8

31. el-Sabbagh AM, Kamel M. Avascular necrosis of temporomandibular joint in sickle cell disease. Clin Rheumatol. 1989;8(3):393-7

32. el Sayed HL, Tawfik ZM. Red cell profile in normal and sickle cell diseased children. J Egypt Soc Parasitol. 1994;24(1):147-54.

33. Kandeel AY, Zimmerman RA, Ohene-Frempong K. Comparison of magnetic resonance angiography and conventional angiography in sickle cell disease: clinical significance and reliability. Neuroradiology. 1996;38(5):409-16.

34. Soliman AT, Bererhi H, Darwish A, Alzalabani MM, Wali Y, Ansari B. Decreased bone mineral density in prepubertal children with sickle cell disease: correlation with growth parameters, degree of siderosis and secretion of growth factors. J Trop Pediatr. 1998;44(4):194-8

35. Moez P, Younan DN. High prevalence of haemoglobin S in the closed Egyptian community of Siwa Oasis. J Clin Pathol. 2016;69(7):632-6.

36. Hamamy HA, Al-Allawi NA. Epidemiological profile of common haemoglobinopathies in Arab countries. J Community Genet. 2013;4(2):147-67.

37. WHO. "Sickle-cell anaemia – Report by the Secretariat" (PDF). Archived from the original (PDF) on 4 January 2011. Retrieved 27 November 2010

38. Adly AA, Ebeid FS. Cultural preferences and limited public resources influence the spectrum of thalassemia in Egypt. J Pediatr Hematol Oncol. 2015;37(4):281-4.

39. Youssry I, Abdel-Salam A, Ismail R, Bou-Fakhredin R, Mohamed Samy R, Ezz El-Deen F, et al. Enhancing Effect of Hydroxyurea on Hb F in Sickle Cell Disease: Ten-Year Egyptian Experience. Hemoglobin. 2017;41(4-6):267-73.

40. Tantawy A, El-Sherif N, Makkeyah S, Eldeen NS, Farghal NBE, Soliman N, et al. Sleep disordered breathing and its relation to stroke and pulmonary hypertension in children with sickle cell disease: a single-center cross-sectional study. Ann Hematol. 2023;102(2):271-81.

41. Ebeid FSE. The implementation of automated red blood cell exchange (erythrocytapheresis) as a treatment modality in sickle cell disease patients: Single center experience. Transfus Apher Sci. 2023;62(4):103719.

42. Kwiatkowski JL, Hamdy M, El-Beshlawy A, Ebeid FSE, Badr M, Alshehri A, et al. Deferiprone vs deferoxamine for transfusional iron overload in SCD and other anemias: a randomized, open-label noninferiority study. Blood Adv. 2022;6(4):1243-54.

43. Hamdy M, El-Beshlawy A, Veríssimo MPA, Kanter J, Inusa B, Williams S, et al. Deferiprone versus deferoxamine for transfusional iron overload in sickle cell disease and other anemias: Pediatric subgroup analysis of the randomized, open-label FIRST study. Pediatr Blood Cancer. 2024;71(1):e30711.

44. Elalfy MS, Hamdy M, El-Beshlawy A, Ebeid FSE, Badr

M, Kanter J, et al. Deferiprone for transfusional iron overload in sickle cell disease and other anemias: open-label study of up to 3 years. Blood Adv. 2023;7(4):611-9.

45. Porter JB, El-Alfy M, Viprakasit V, Giraudier S, Chan LL, Lai Y, et al. Utility of labile plasma iron and transferrin saturation in addition to serum ferritin as iron overload markers in different underlying anemias before and after deferasirox treatment. Eur J Haematol. 2016;96(1):19-26.

46. Maggio A, Kattamis A, Felisi M, Reggiardo G, El-Beshlawy A, Bejaoui M, et al. Evaluation of the efficacy and safety of deferiprone compared with deferasirox in paediatric patients with transfusion-dependent haemoglobinopathies (DEEP-2): a multicentre, randomised, open-label, non-inferiority, phase 3 trial. Lancet Haematol. 2020;7(6):e469-e478.

47. Aljurf M, Nassar A, Hamidieh AA, Elhaddad A, Hamladji RM, Bazarbachi A, et al. Hematopoietic stem cell transplantation in the Eastern Mediterranean Region (EMRO) 2011-2012: A comprehensive report on behalf of the Eastern Mediterranean Blood and Marrow Transplantation group (EMBMT). Hematol Oncol Stem Cell Ther. 2015;8(4):167-75.

48. Ebeid FSE, Aly NH, Shaheen NM, Abdellatif SMA, Okba AAM, Gad NA, et al. Safety and efficacy of L-Glutamine in reducing the frequency of acute complications among patients with sickle cell disease: A randomized controlled study. Ann Hematol. 2024;103(9):3493-506.

49. Vichinsky E, Hoppe CC, Ataga KI, Ware RE, Nduba V, El-Beshlawy A, et al. A Phase 3 Randomized Trial of Voxelotor in Sickle Cell Disease. N Engl J Med. 2019;381(6):509-19.

50. Howard J, Ataga KI, Brown RC, Achebe M, Nduba V, El-Beshlawy A, et al. Voxelotor in adolescents and adults with sickle cell disease (HOPE): long-term follow-up results of an international, randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Haematol. 2021;8(5):e323-e333.

51. Pfizer. https://www.pfizer.com/news/press-release/press-release-detail/pfizer-voluntarily-withdraws-all-lots-sickle-cell-disease. Accessed on 25 Sep 2024.

52. Heeney MM, Hoppe CC, Abboud MR, Inusa B, Kanter J, Ogutu B, et al. A Multinational Trial of Prasugrel for Sickle Cell Vaso-Occlusive Events. N. Engl. J. Med. 2016;374(7):625-35.

53. Heath LE, Heeney MM, Hoppe CC, Adjei S, Agbenyega T, Badr M, et al. Successful utilization of an electronic pain diary in a multinational phase 3 interventional study of pediatric sickle cell anemia. Clin Trials. 2017;14(6):563-71.

54. De Montalembert M, Abboud MR, Fiquet A, Inati A, Lebensburger JD, Kaddah N, et al. 13-valent pneumococcal conjugate vaccine (PCV13) is immunogenic and safe in children 6-17 years of age with sickle cell disease previously vaccinated with 23-valent pneumococcal polysaccharide vaccine (PPSV23): Results of a phase 3 study. Pediatr Blood Cancer. 2015;62(8):1427-36.

55. Abdelhalim SM, Murphy JE, Meabed MH, Elberry AA, Gamaleldin MM, Shaalan MS, Hussein RRS. Comparative effectiveness of adding Omega-3 or Vitamin D to standard therapy in preventing and treating episodes of painful crisis in pediatric sickle cell patients. Eur Rev Med Pharmacol Sci. 2022;26(14):5043-52.