Scientific Journal of
Neurology & Neurosurgery

Case Report

Problematic of Treatment in the Acute Stage of Stroke in Sickle Cell Patients in Semi-Urban Areas: Experience of CHU Kara (Togo) About 2 Patients and Literature Review -

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Submitted: 09 October 2021; **Approved:** 16 October 2021; **Published:** 20 October 2021

Cite this article: Léhleng AGBA, Kombate D, Anayo N, Kumako V, Guinhouya KM, Apetse K, Talabewi A, Assogba K, Dagbe M, Belo M, Balogou A. Problematic of Treatment in the Acute Stage of Stroke in Sickle Cell Patients in Semi-Urban Areas: Experience of CHU Kara (Togo) About 2 Patients and Literature Review. Sci J Neurol Neurosurg. 2021; Oct 20; 7(1): 019-024.

ISSN: 2640-5733

ISSN: 2640-5733

ABSTRACT

Sickle Cell Disease (SCD) is the most common inherited disorder in sub-Saharan Africa. Cerebrovascular accident is a catastrophic complication of SCD and a leading cause of death in both children and adults. If in developed countries, diagnosis and treatment of strokes in SCD patients have evolved well, this is not the case in low-income countries. From 2 cases, we reported the technical means at our disposal for the management of this type of stroke in semi-urban areas such as the city of Kara.

Keywords: Stroke; Sickle cell disease; CHU Kara; Togo

INTRODUCTION

Sickle Cell Disease (SCD) is the most common inherited disorder in Sub-Saharan Africa (SSA) [1] and is recognized by the World Health Organization as a global public health concern [2]. Cerebrovascular Accident (CVA) is a catastrophic complication of SCD and a leading cause of death in both children [3] and adults [4]. The reported risk of first CVA in the first 20 years of life is 0.761 per 100 patient-years [5]. In developing countries, studies are available on the different aspects of stroke in sickle cell. For example, recent data on prevalence and incidence have been obtained from the Cooperative Study of Sickle Cell Disease (CSSCD) of more than 4000 patients with SCD observed in 23 US clinical centers over 10-year period [6]. In Sub-Saharan Africa, few studies are available and mainly concern pediatric cases [7-9]. Although publications have been made in Togo on sickle cell disease [10-12], none reports neurological complications such as stroke and their management. We report two cases of strokes in SCD and the particularity of their management in a center of limited technical tray.

CASE REPORTS

Case 1

A 25-year-old women right-handed, with sickle cell disease hemoglobin SC, without follow-up, transferred from the gynecology-obstetrics department to the medical department on April 03, 2019 for a left sided deficit that occurred on the third day of a cesarean section. There was no history of heart disease, hypertension, diabetes mellitus, oral contraceptive intake, smoking or stroke. She is primigest and primiparous. She had a cesarean section three days earlier at 34 weeks of amenorrhea following an episode of vaso-occlusive crisis. When she was admitted to the medical department, she had a good general condition, an axillary temperature of 38°C, a blood pressure of 124/80 mm Hg, a weight of 65 kg and a height of 167 cm, corresponding to a Body Mass Index (BMI) of 23.3kgm^{-2}. Neurologically, she was conscious, vigilant with no memory or language impairment. There was left visuospatial neglect and left hemiasomatognosia; an acute left pyramidal syndrome predominantly brachio-facial with a muscle strength of 0/5 in the upper limb and 2/5 in the lower limb, tactile and thermoalgic hypoesthesia of the left half body as well as impairment of the deep sensitivity of the left half body. Examination of the cranial nerves revealed a Homonymous Left Lateral Hemianopia (HLH) without involvement of extrinsic or intrinsic oculomotricity, a left central facial palsy. There was no sign of Claude Bernard Horner Syndrome (CBH). Heart sounds were steady at 102 beats per minute (bpm) with no murmur. Peripheral pulses were synchronous with the heart sounds. There was no peripheral sign of heart failure or phlebitis. Lung auscultation was normal. The examination of the digestive, splenoganglionic, otorhino-laryngologic, urogenital, skin and integuments systems was normal. The operative wound was clean. The brain CT scan without injection revealed a zone of right triangular fronto-parietal hypodensity forming part of an ischemic stroke in the acute phase of the superficial territory of the right Middle Cerebral Artery (MCA) (Figure 1). The complete blood count showed neutrophilia at 15,200 per mm^3 associated with anemia at 7 g/dl, a Mean Corpuscular Hemoglobin (MCH) at 21 pg, a Mean Corpuscular Hemoglobin Concentration (MCHC) at 17 mmol/l and a Mean Corpuscular Volume (MCV) at 67 fl. The Erythrocyte Sedimentation Rate (ESR) was 62 mm. Plasma glucose level, renal and hepatic functions, plasma electrolyte levels, total cholesterol and its fractions were without abnormalities. Serologies of hepatitis viral markers and Human Immunodeficiency Virus (HIV) were negatives as well as syphilis serology (TPHA-VDRL). The Electrocardiogram (ECG) was recorded in sinus rhythm at 102 bpm. A Transthoracic Echocardiography (TTE) and a doppler study of neck vessels were normal. Sickle cell disease hemoglobin SC has been identified as the etiology of stroke in this patient. She had transfusion exchanges in the form of bloodletting-transfusion in association with hyperhydration. She was receiving enoxaparin 0.4 ml per day and an antiplatelet drug (Kardegic 160 mg per day) with prevention of a stress ulcer with 40 mg omeprazole per day. Physiotherapy and psychotherapy have been done. Antibiotic administration (Ofloxacin 200 mg every 12 hours) has been done in this context of fever and neutrophilia. The clinical course was a recovery of motor skills which was 2/5 in the upper limb and 4/5 in the lower limb on the 9th day. The biological inflammatory syndrome normalized within one week but ofloxacin was continued orally for 3 weeks. She was discharged after 12 days of hospitalization with a Rankin score of 2/5. The transfusion program was continued. At 3 months, the motor skill was 4/5 in the left limbs with a Rankin score at 90 days of 1/5. Follow-up with a hematologist was recommended.

Case 2

10-year-old patient, right-handed student, admitted in the pediatric department of Kara Teaching Hospital on August 19,

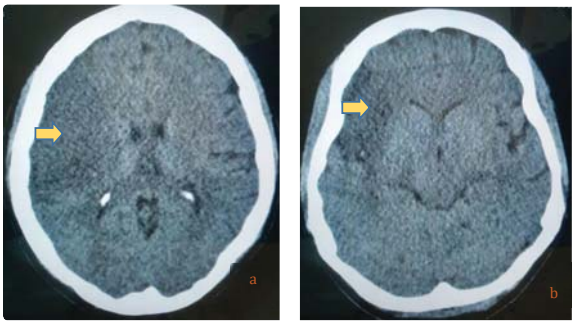

Figure 1: Non-contrast CT showed territorial infarction in the right middle cerebral artery territory from the insular/perisylvian to the fronto parietal cortex involving mainly the superior division of the MCA but sparing the lenticulostriate territory.

2018 for a sudden motor deficit of the right half-body associated with a language disorder 24 hours before her admission. She had been receiving treatment for an acute respiratory infection with antibiotic (amoxicillin-clavulanic acid and ciprofloxacin) a week earlier. On the sixth day of her treatment, she reported a heaviness in her right half-body which rapidly worsened and then followed a speech disorder. The patient is known for homozygous sickle cell anemia (SS) and is monitored regularly by a hematologist. There was no other associated comorbidity. His vaccination was up to date. On examination, she was in good general condition, had 38.2°C of temperature. She had normal consciousness and an aphasia, Broca's type. There was a predominantly brachiofacial right acute pyramidal syndrome with a force of 3/5 in the upper limb and 5/5 in the lower limb. Deep tendon reflexes were reduced on the right side and the ipsilateral plantar cutaneous reflex was indifferent. Tactile and thermoalgic hyposesthesia without impairment of deep sensitivity was present in the right hemibody. Examination of the cranial nerves revealed right HLH. There was no meningeal syndrome. The heart rate was regular and synchronized with the peripheral pulses. There was no heart murmur. Lung auscultation was normal. The brain CT scan performed 48 hours after the deficit showed a left frontal ischemia corresponding to the territory of the superficial branch of the left Sylvian artery, in particular the M3 segment (Figure 2). The ECG was normal. Laboratory tests showed high gamma globulin levels, C-Reactive Protein (CRP) at 24 mg/l, an ESR at 63 mm at the first hour, microcytic anemia with the rate of hemoglobin at 6.2 g/dl. A TTE did not show any abnormalities of the heart cavities or myocardium. Bacteriological Examination of Urine (BEU) and blood culture were negative. Hemoglobinopathy has been identified as the etiology of this stroke. She received antiplatelet therapy with Kardegic 75 mg per day, enoxaparin 0.4 ml per day, physiotherapy, speech therapy and psychological support. Transfusion exchange sessions were held. Systematic hyperhydration and analgesic with paracetamol 15 mg/kg every 6 hours. Apart from the inflammatory syndrome which may be related to the sickling, the pre-existing respiratory infection before her admission and the fever motivated the continuation of the antibiotic therapy with Ofloxacin at a dose of 15 mg per day in 2 administrations. The clinical course was good with almost complete recovery of speech and motor skills in the right upper limb at day 6. The biological inflammatory syndrome normalized within one week but ofloxacin was continued orally for 15 days. She was discharged after 16 days in hospital with a Rankin score of 1/5. The transfusion program was continued. At 3 months of the episode, speech was normal, motor skills of the upper right limb restored except for dexterity when writing. The 90-day Rankin was 0/5. Follow-up by the hematologist should be continued.

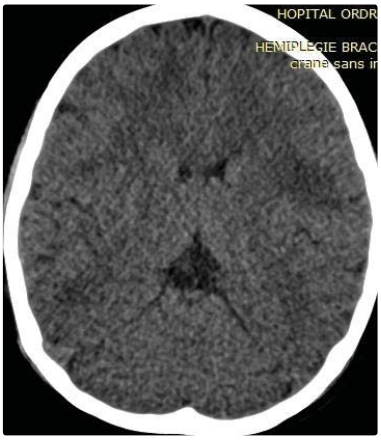

Figure 2: Non-contrast cranial CT scan showed small infarct in the left middle cerebral artery territory involving one of superficial branches.

DISCUSSION

We have reported 2 cases of stroke in patients with SCD, double heterozygous SC for one and homozygous SS for the other. The two patients are female, aged 10 and 25. In both cases, it was an ischemic stroke. Indeed, in regions where the condition is prevalent, including Africa and parts of the USA and Europe, SCD is typically the most common cause of overt stroke in children [13-15]. Adults with SCD are also affected, with rising prevalence and incidence with age [16-18]. Marks LJ, et al. [7] reported in 2018, after a systematic review of the literature that approximately 60 000 children in SSA have strokes related to SCD. Early studies found that approximately 75% of the strokes were ischemic and the remainder were hemorrhagic [19]. This large predominance of ischemic stroke is also revealed by our study. The prevalence of CVA in all forms of SCD (HbSS, HbSC, HbSβ thalassaemia) was 3.75% overall, ranging from 0.11% in those under 2 years old to 7.62% of those aged 40-49 years [20]. This prevalence is variable. In France the prevalence was 3.2% in those with HbSS, 1.2% in HbSC patients [21]. In a Brazilian, the overall prevalence of overt stroke was 5.1% (3-7.2%) [22]. In some countries of SSA like Cameroon, Kenya, Nigeria, the prevalence of stroke relative to SCD was respectively 6.7%, 3.3% and 9.1% [23-25]. In terms of pathophysiology, the understanding of the mechanism of stroke in sickle cell disease has evolved considerably. For ischemic stroke, it was traditionally hypothesized to be due to increased viscosity of sickled red blood cells causing stasis and downstream ischemia. However, this hypothesis does not fully explain the etiology of the large vessel CVAs that mark this disease. Current research suggests that early events in the pathogenesis of stroke are the attachment of sickled cells to vascular endothelium where endothelial activation and damage occur [26]. Patients with SCD have been shown to have high expression of endothelial and erythrocyte adhesion molecules [27]. Procoagulants, such as von Willebrand factor [28], fibrinogen [29] and thrombin [30], have also been implicated. Chemoattractants, cytokines and adhesion molecules recruit leukocytes that can cause microvascular obstruction and ischemia [31-32]. This proinflammatory state leads to intimal hyperplasia, fibrosis and, ultimately, thrombosis [26]. Additional research has implicated Nitric Oxide (NO) and NO-related pathways as part of the pathophysiology of stroke. For hemorrhagic stroke, imaging studies have demonstrated a high prevalence of cerebral vasculopathy in patients with SCD. The latter have been shown to develop cerebral aneurysms, although their exact prevalence is unknown. Aneurysms are the most common identified cause of hemorrhagic stroke in adult patients with SCD [33]. Compared with patients without SCD, aneurysms in SCD patients are often multiple, have an increased propensity for the posterior cerebral circulation and may be prone to rupture at smaller sizes [34]. Patients with SCD are also subject to silent infarcts. Their pathogenesis is different from ischemic or hemorrhagic strokes as they involve small vessels in watershed distributions instead of the larger cerebral vessels [35]. However, these theories are under active research. The diagnosis of stroke in sickle cell patients is identical to that of non-sickle cell patients. It is mentioned in the clinic when a focal neurologic deficit sets suddenly. Cerebral imaging, CT scan or MRI can be used to confirm this diagnosis. However, CT scans are limited in their ability to detect acute infarct [36]. In our context with

limited resources and insufficient infrastructure, our 2 patients only performed the cerebral CT scan which, however, made it possible to identify the ischemia. Apart from this imaging, other ancillary tests must be carried out at the acute stage of the stroke. Initial laboratory evaluation should include a complete blood count with differential and reticulocyte count, coagulation studies, hemoglobin quantification to determine the hemoglobin S percent, blood chemistries and evaluation for meningitis if clinically indicated. The patient's blood should be typed and screened for any red blood cell antibodies. If there is enough clinical concern, MRI/MRA/ magnetic resonance venography with diffusion-weighted imaging is the preferred modality for evaluating ischemic stroke, vasculopathy and eliminating dural venous sinus thrombosis as the etiology of the event [37]. Intravenous fluids should be carefully monitored to maintain euvolemia. Additional supportive care measures to control glucose, maintain cerebral perfusion pressure and reduce fever should be performed. Currently, there is no role for anticoagulation or antifibrinolytics as they have not been studied in patients with SCD and may increase the risk of hemorrhagic conversion [36]. A manual or automated exchange transfusion should be performed with a goal of decreasing the hemoglobin S to below 30% and increasing the hemoglobin to 10-12 g/dl to improve oxygen carrying capacity [38]. The manual transfusion exchanges of our patients were not followed by monitorring of the level of hemoglobin S because of the long time usually necessary to obtain the results of the electrophoresis of hemoglobin in our hospital practice. However, the hyperhydradation was done in order to reduce blood viscosity. The absence of a sickle cell crisis or other complication suggests that our treatment had a positive effect on the outcome. For the secondary stroke prevention, Chronic Transfusion Therapy (CTT) has long been used. Transfusions are generally administered every 3-4 weeks with the goal to maintain the hemoglobin S under 30% of the total hemoglobin. Without treatment, the risk of recurrent stroke is approximately 70% [33], but with CTT, that risk is reduced to 10-20% [39-41]. Attempts to discontinue CTT after periods of up to 10-12 years resulted in a high rate of recurrent stroke, so lifelong treatment is recommended [42]. It is well known that CTT is complicated by potential risks of alloimmunization [43], infectious disease exposure [44] and iron overload [45]. It is with this in mind that we have not continued the transfusion exchanges in our patients since we do not have the necessary equipment to monitor the iron load and the risk of related alloimmunization. An antiplatelet aggregant has been used in our patients for secondary prevention. Long-term follow-up with a hematologist was recommended in order to put them on Hydroxycarbamide, a treatment that the two patients did not have before the stroke episode. Single institutions have explored hydroxyurea as an alternative therapy for secondary stroke prevention in pediatric patients with SCD in countries where blood products are scarce. One institution in Jamaica followed 43 children with SCD with evidence of acute ischemic stroke between 2000 and 2009 [46]. Of these, ten initiated therapy with hydroxyurea alone. In those patients, the incidence of recurrent stroke was two per 100 person-years, compared with 29 per 100 person-years in the untreated group [46]. The place of Transcranial Doppler (TCD) is very important in the management of stroke in patients with SCD at all stages. It makes it possible to detect subjects at risk, to make the etiological diagnosis in addition to the scan or MRI and to follow up as a preventive measure [47].

CONCLUSION

Strokes cause significant morbidity and mortality in pediatric patients with SCD. Unscreened or unmonitored pediatric patients constitute a group at high risk of cardiovascular accident, including stroke. Fortunately, transcranial doppler can identify children at high risk of developing ischemic stroke and chronic transfusion therapy is very effective at preventing stroke in the high-risk group. This study calls on us to make another more extensive one by monitoring sickle cell patients benefiting from care in a suitable structure.

REFERENCES

1. Piel FB, Patil AP, Howes RE, Nyangiri OA, Gething PW, Dewi M, Temperley WH, Williams TN, Weatherall DJ, Hay SI. Global epidemiology of sickle haemoglobin in neonates: A contemporary geostatistical model-based map and population estimates. Lancet. 2013 Jan 12;381(9861):142-51. doi: 10.1016/S0140-6736(12)61229-X. Epub 2012 Oct 25. PMID: 23103089; PMCID: PMC3547249.
2. World health organization regional office for Africa. Sickle-cell disease: A strategy for the WHO African region: Report of the regional director (AFR/ RC60/68). Geneva, Switzerland: World health organization; 2010. https:// tinyurl.com/nfhjesxc
3. Leikin SL, Gallagher D, Kinney TR, Sloane D, Klug P, Rida W. Mortality in children and adolescents with sickle cell disease. Cooperative Study of Sickle Cell Disease. Pediatrics. 1989 Sep;84(3):500-8. PMID: 2671914.
4. Platt OS, Brambilla DJ, Rosse WF, Milner PF, Castro O, Steinberg MH, Klug PP. Mortality in sickle cell disease. Life expectancy and risk factors for early death. N Engl J Med. 1994 Jun 9;330(23):1639-44. doi: 10.1056/ NEJM199406093302303. PMID: 7993409.
5. Powars D, Wilson B, Imbus C, Pegelow C, Allen J. The natural history of stroke in sickle cell disease. Am J Med. 1978 Sep;65(3):461-71. doi: 10.1016/0002-9343(78)90772-6. PMID: 717414.
6. Ohene-Frempong K, Weiner SJ, Sleeper LA, Miller ST, Embury S, Moohr JW, Wethers DL, Pegelow CH, Gill FM. Cerebrovascular accidents in sickle cell disease: Rates and risk factors. Blood. 1998 Jan 1;91(1):288-94. PMID: 9414296.
7. Marks LJ, Munube D, Kasirye P, Mupere E, Jin Z, LaRussa P, Idro R, Green NS. Stroke Prevalence in Children With Sickle Cell Disease in Sub-Saharan Africa: A Systematic Review and Meta-Analysis. Glob Pediatr Health. 2018 May 14;5:2333794X18774970. doi: 10.1177/2333794X18774970. PMID: 29785408; PMCID: PMC5954575.
8. Abdullahi SU, DeBaun MR, Jordan LC, Rodeghier M, Galadanci NA. Stroke Recurrence in Nigerian Children With Sickle Cell Disease: Evidence for a Secondary Stroke Prevention Trial. Pediatr Neurol. 2019 Jun;95:73-78. doi: 10.1016/j.pediatrneurol.2019.01.008. Epub 2019 Jan 17. PMID: 30952488; PMCID: PMC6529264.
9. Napon C, Kaboré A, Ouédraogo M, Dravé A, Lompo L, Kaboré J. Accidents vasculaires cérébraux et hémoglobinopathies au Burkina Faso [Strokes and hemoglobinopathies in Burkina Faso]. Med Sante Trop. 2012 Oct-Dec;22(4):390-3. French. doi: 10.1684/mst.2012.0107. PMID: 23360985.
10. Guédéhoussou T, Gbadoé AD, Lawson-Evi K, Atakouma DY, Ayikoé AK, Vovor A, Tatagan-Agbi K, Assimadi JK. Connaissances de la drépanocytose et pratiques de prévention dans la population d'un district urbain de Lomé, Togo [Knowledge of sickle cell disease and prevention methods in an urban district of Lomé, Togo]. Bull Soc Pathol Exot. 2009 Oct;102(4):247-51. French. PMID: 19950543.
11. Gbadoé AD, Atsou K, Agbodjan-Djossou OA, Tsolényanu E, Nyadanu M, Dogba AD, Assimadi JK. Prise en charge ambulatoire des drépanocytaires: évaluation de la première année de suivi des patients dans le service de pédiatrie de Lomé (Togo) [Ambulatory management of sickle cell disease: evaluation of the first year follow up of patients in the pediatric department of Lomé (Togo)]. Bull Soc Pathol Exot. 2001 May;94(2):101-5. French. PMID: 11475024.
12. Akakpo-Numado GK, Gnassingbé K, Abalo A, Boume MA, Sakiye KA, Tekou H. Locations of osteomyelitis in children with sickle-cell disease at

Tokoin teaching hospital (Togo). Pediatr Surg Int. 2009 Aug;25(8):723-6. doi: 10.1007/s00383-009-2410-2. Epub 2009 Jul 2. PMID: 19572137.

13. Obama MT, Dongmo L, Nkemayim C, Mbede J, Hagbe P. Stroke in children in Yaounde, Cameroon. Indian Pediatr. 1994 Jul;31(7):791-5. PMID: 7890341.

14. Macharia AW, Mochamah G, Uyoga S, Ndila CM, Nyutu G, Makale J, Tendwa M, Nyatichi E, Ojal J, Shebe M, Awuondo KO, Mturi N, Peshu N, Tsofa B, Scott JAG, Maitland K, Williams TN. The clinical epidemiology of sickle cell anemia In Africa. Am J Hematol. 2018 Mar;93(3):363-370. doi: 10.1002/ajh.24986. Epub 2017 Dec 18. PMID: 29168218; PMCID: PMC6175377.

15. Earley CJ, Kittner SJ, Feeser BR, Gardner J, Epstein A, Wozniak MA, Wityk R, Stern BJ, Price TR, Macko RF, Johnson C, Sloan MA, Buchholz D. Stroke in children and sickle-cell disease: Baltimore-Washington cooperative young stroke study. Neurology. 1998 Jul;51(1):169-76. doi: 10.1212/wnl.51.1.169. PMID: 9674798.

16. Ohene-Frempong K, Weiner SJ, Sleeper LA, Miller ST, Embury S, Moohr JW, Wethers DL, Pegelow CH, Gill FM. Cerebrovascular accidents in sickle cell disease: Rates and risk factors. Blood. 1998 Jan 1;91(1):288-94. PMID: 9414296.

17. Strouse JJ, Jordan LC, Lanzkron S, Casella JF. The excess burden of stroke in hospitalized adults with sickle cell disease. Am J Hematol. 2009 Sep;84(9):548-52. doi: 10.1002/ajh.21476. PMID: 19623672; PMCID: PMC2737603.

18. Strouse JJ, Lanzkron S, Urrutia V. The epidemiology, evaluation and treatment of stroke in adults with sickle cell disease. Expert Rev Hematol. 2011 Dec;4(6):597-606. doi: 10.1586/ehm.11.61. PMID: 22077524; PMCID: PMC3267235.

19. Powars D, Wilson B, Imbus C, Pegelow C, Allen J. The natural history of stroke in sickle cell disease. Am J Med. 1978 Sep;65(3):461-71. doi: 10.1016/0002-9343(78)90772-6. PMID: 717414.

20. Ohene-Frempong K, Weiner SJ, Sleeper LA, Miller ST, Embury S, Moohr JW, Wethers DL, Pegelow CH, Gill FM. Cerebrovascular accidents in sickle cell disease: rates and risk factors. Blood. 1998 Jan 1;91(1):288-94. PMID: 9414296.

21. de Montalembert M, Guilloud-Bataille M, Feingold J, Girot R. Epidemiological and clinical study of sickle cell disease in France, French Guiana and Algeria. Eur J Haematol. 1993 Sep;51(3):136-40. doi: 10.1111/j.1600-0609.1993.tb00613.x. PMID: 8405327.

22. Belisário AR, Nogueira FL, Rodrigues RS, Toledo NE, Cattabriga AL, Velloso-Rodrigues C, Duarte FO, Silva CM, Viana MB. Association of alpha-thalassemia, TNF-alpha (-308G>A) and VCAM-1 (c.1238G>C) gene polymorphisms with cerebrovascular disease in a newborn cohort of 411 children with sickle cell anemia. Blood Cells Mol Dis. 2015 Jan;54(1):44-50. doi: 10.1016/j.bcmd.2014.08.001. Epub 2014 Aug 27. PMID: 25175566.

23. Njamnshi AK, Mbong EN, Wonkam A, Ongolo-Zogo P, Djientcheu VD, Sunjoh FL, Wiysonge CS, Sztajzel R, Mbanya D, Blackett KN, Dongmo L, Muna WF. The epidemiology of stroke in sickle cell patients in Yaounde, Cameroon. J Neurol Sci. 2006 Dec 1;250(1-2):79-84. doi: 10.1016/j.jns.2006.07.003. Epub 2006 Aug 14. PMID: 16905153.

24. Amayo EO, Owade JN, Aluoch JR, Njeru EK. Neurological complications of sickle cell anaemia at KNH: a five year retrospective study. East Afr Med J. 1992 Dec;69(12):660-2. PMID: 1298628.

25. Lagunju IA, Brown BJ. Adverse neurological outcomes in Nigerian children with sickle cell disease. Int J Hematol. 2012 Dec;96(6):710-8. doi: 10.1007/s12185-012-1204-9. Epub 2012 Nov 6. PMID: 23129067.

26. Platt OS. Preventing stroke in sickle cell anemia. N Engl J Med. 2005 Dec 29;353(26):2743-5. doi: 10.1056/NEJMp058274. PMID: 16382060.

27. Frenette PS. Sickle cell vaso-occlusion: multistep and multicellular paradigm. Curr Opin Hematol. 2002 Mar;9(2):101-6. doi: 10.1097/00062752-200203000-00003. PMID: 11844991.

28. Kaul DK, Nagel RL, Chen D, Tsai HM. Sickle erythrocyte-endothelial interactions in microcirculation: the role of von Willebrand factor and implications for vasoocclusion. Blood. 1993 May 1;81(9):2429-38. PMID: 8481522.

29. Wautier JL, Pintigny D, Wautier MP, Paton RC, Galacteros F, Passa P, Caen JP. Fibrinogen, a modulator of erythrocyte adhesion to vascular endothelium. J Lab Clin Med. 1983 Jun;101(6):911-20. PMID: 6854127.

30. Ataga KI, Moore CG, Hillery CA, Jones S, Whinna HC, Strayhorn D, Sohier C, Hinderliter A, Parise LV, Orringer EP. Coagulation activation and inflammation in sickle cell disease-associated pulmonary hypertension. Haematologica. 2008 Jan;93(1):20-6. doi: 10.3324/haematol.11763. PMID: 18166781.

31. Okpala I. Leukocyte adhesion and the pathophysiology of sickle cell disease. Curr Opin Hematol. 2006 Jan;13(1):40-4. doi: 10.1097/01.moh.0000190108.62414.06. PMID: 16319686.

32. Frenette PS. Sickle cell vasoocclusion: heterotypic, multicellular aggregations driven by leukocyte adhesion. Microcirculation. 2004 Mar;11(2):167-77. PMID: 15280090.

33. Powars D, Wilson B, Imbus C, Pegelow C, Allen J. The natural history of stroke in sickle cell disease. Am J Med. 1978 Sep;65(3):461-71. doi: 10.1016/0002-9343(78)90772-6. PMID: 717414.

34. Brandão RA, de Carvalho GT, Reis BL, Bahia E, de Souza AA. Intracranial aneurysms in sickle cell patients: report of 2 cases and review of the literature. Surg Neurol. 2009 Sep;72(3):296-9; discussion 299. doi: 10.1016/j.surneu.2008.03.044. Epub 2008 Jul 9. PMID: 18614211.

35. Pegelow CH, Wang W, Granger S, Hsu LL, Vichinsky E, Moser FG, Bello J, Zimmerman RA, Adams RJ, Brambilla D; STOP Trial. Silent infarcts in children with sickle cell anemia and abnormal cerebral artery velocity. Arch Neurol. 2001 Dec;58(12):2017-21. doi: 10.1001/archneur.58.12.2017. PMID: 11735775.

36. Webb J, Kwiatkowski JL. Stroke in patients with sickle cell disease. Expert Rev Hematol. 2013 Jun;6(3):301-16. doi: 10.1586/ehm.13.25. PMID: 23782084.

37. Steen RG, Reddick WE, Mulhern RK, Langston JW, Ogg RJ, Bieberich AA, Kingsley PB, Wang WC. Quantitative MRI of the brain in children with sickle cell disease reveals abnormalities unseen by conventional MRI. J Magn Reson Imaging. 1998 May-Jun;8(3):535-43. doi: 10.1002/jmri.1880080304. PMID: 9626865.

38. Hulbert ML, Scothorn DJ, Panepinto JA, Scott JP, Buchanan GR, Sarnaik S, Fallon R, Chu JY, Wang W, Casella JF, Resar L, Berman B, Adamkiewicz T, Hsu LL, Smith-Whitley K, Mahoney D, Woods G, Watanabe M, DeBaun MR. Exchange blood transfusion compared with simple transfusion for first overt stroke is associated with a lower risk of subsequent stroke: a retrospective cohort study of 137 children with sickle cell anemia. J Pediatr. 2006 Nov;149(5):710-2. doi: 10.1016/j.jpeds.2006.06.037. PMID: 17095350.

39. Sarnaik S, Soorya D, Kim J, Ravindranath Y, Lusher J. Periodic transfusions for sickle cell anemia and CNS infarction. Am J Dis Child. 1979 Dec;133(12):1254-7. doi: 10.1001/archpedi.1979.02130120046009. PMID: 517476.

40. Scothorn DJ, Price C, Schwartz D, Terrill C, Buchanan GR, Shurney W, Sarniak I, Fallon R, Chu JY, Pegelow CH, Wang W, Casella JF, Resar LS, Berman B, Adamkiewicz T, Hsu LL, Ohene-Frempong K, Smith-Whitley K, Mahoney D, Scott JP, Woods GM, Watanabe M, Debaun MR. Risk of recurrent stroke in children with sickle cell disease receiving blood transfusion therapy for at least five years after initial stroke. J Pediatr. 2002 Mar;140(3):348-54. doi: 10.1067/mpd.2002.122498. PMID: 11953734.

41. Pegelow CH, Adams RJ, McKie V, Abboud M, Berman B, Miller ST, Olivieri N, Vichinsky E, Wang W, Brambilla D. Risk of recurrent stroke in patients with sickle cell disease treated with erythrocyte transfusions. J Pediatr. 1995 Jun;126(6):896-9. doi: 10.1016/s0022-3476(95)70204-0. PMID: 7776091.

42. Wang WC, Kovnar EH, Tonkin IL, Mulhern RK, Langston JW, Day SW, Schell MJ, Wilimas JA. High risk of recurrent stroke after discontinuance of five to twelve years of transfusion therapy in patients with sickle cell disease.

J Pediatr. 1991 Mar;118(3):377-82. doi: 10.1016/s0022-3476(05)82150-x. PMID: 1999776.

43. Venkateswaran L, Teruya J, Bustillos C, Mahoney D Jr, Mueller BU. Red cell exchange does not appear to increase the rate of allo- and auto-immunization in chronically transfused children with sickle cell disease. Pediatr Blood Cancer. 2011 Aug;57(2):294-6. doi: 10.1002/pbc.22985. Epub 2011 Feb 4. PMID: 21298771.

44. Vichinsky EP. Current issues with blood transfusions in sickle cell disease. Semin Hematol. 2001 Jan;38(1 Suppl 1):14-22. doi: 10.1016/s0037-1963(01)90056-3. PMID: 11206956.

45. Fung EB, Harmatz P, Milet M, Ballas SK, De Castro L, Hagar W, Owen W, Olivieri N, Smith-Whitley K, Darbari D, Wang W, Vichinsky E; Multi-Center Study of Iron Overload Research Group. Morbidity and mortality in chronically transfused subjects with thalassemia and sickle cell disease: A report from the multi-center study of iron overload. Am J Hematol. 2007 Apr;82(4):255-65. doi: 10.1002/ajh.20809. PMID: 17094096.

46. Ali SB, Moosang M, King L, Knight-Madden J, Reid M. Stroke recurrence in children with sickle cell disease treated with hydroxyurea following first clinical stroke. Am J Hematol. 2011 Oct;86(10):846-50. doi: 10.1002/ajh.22142. Epub 2011 Sep 2. PMID: 21898530.

47. Kirkham FJ, Lagunju IA. Epidemiology of Stroke in Sickle Cell Disease. J Clin Med. 2021 Sep 18;10(18):4232. doi: 10.3390/jcm10184232. PMID: 34575342; PMCID: PMC8469588.