Stroke in children with sickle cell anaemia in Sokoto: a ten-year review

Jiya, N M, *Ahmad M M and Baba, J

Original Article

ABSTRACT

Objective: Stroke (cerebrovascular accident) generally occurs more often in children than once suspected, with its attendant potential consequences. It is an under recognized cause of neurologic disabilty in children, with varied causes. Stroke is a devastating and potentially life threatening complication of sickle cell anaemia (SCA). Children with sickle cell haemoglobinopathy have a life time increased risk of developing a stroke. This study aims to assess the pattern of stroke presentation among SCA children in Sokoto, North-Western Nigeria.

Methodology: A review of all the clinical records of children with SCA who were diagnosed and managed for sickle cell related stroke at Usmanu Danfodiyo University Teaching Hospital (UDUTH) Sokoto; Nigeria, over a ten-year period (May, 2004 – April, 2014) was undertaken. Data analysis was done using the statistical package for social sciences (SPSS) version 20.

Results: Fifteen cases of Paediatrics stroke were identified, out of a total of 416 registered children with SCA, giving a stroke prevalence of 3.6%. Male: Female ratio was 1:1. All the stroke cases were of haemoglobin SS electrophoresis; with a mean age at diagnosis of SCA of 2.2 (±1.5) years and mean age at stroke onset of 6.3 (±2.8) years. Mean time of hospital presentation after the stroke onset was 10 (±2.5) days. Hemiparesis and expressive aphasia were the predominant presenting features. Based on the neuroimaging findings, majority of the stroke types were infarctive (71.4%). No mortality was recorded.

Conclusion: The prevalence of sickle cell related childhood stroke of 3.6% in this series is relatively low. Majority of the patients presented to hospital very late, after the stroke onset. There is therefore the need for increased awareness on childhood stroke in our community, in order to facilitate early hospital presentation and prompt management to improve the outcome.

Key words: Paediatric stroke, Sickle cell anaemia, Late Presentation, Outcome

*Corresponding author: Dr Ahmad Muhammad Murtala, E-mail: murisbn@yahoo.com.
Department of Paediatrics, Usmanu Danfodiyo University Teaching Hospital Sokoto, Nigeria

La maladie de course chez les enfants atteints d'anémie falciforme à Sokoto: Un examen décennal

Jiya, N M, *Ahmad M M and Baba, J

Article Original

RÉSUMÉ

Objectif: AVC (Accident Vasculaire Cérébral) se produit généralement plus souvent chez les enfants soupçoonés, avec ses conséquences potentielles en découlent, c'est une cause et vertu reconnues d'invalidité neurologique dévastatrice et potentiellement mortelle complication très grave d'anémie falciforme (AF). Les enfants atteints de drépanocytetosse hémoglobinopathie ont une durée de vie risquée accrue de développer un accident vasculaire cérébral. Cette étude vise à évaluer le modelé de présentation de l'AVC chez les enfants de SCA à Sokoto, au nord-sud et du Nigeria.

Méthodes: Un examen de tous les dossiers cliniques des enfants atteints de SCA qui ont été d'agnosiques et gères pour drépanocytose AVC liés à Sokoto Hôpital Universitaire d'Enseignement d' Usman Danfodiyo, Nigeria sur une période de dix-ans (mai 2004 – Avril, 2004) a été entrepris. L'analyse des données a été faite en utilisant le logiciel de statistiques pour les sciences sociales (LSSS) la version 20.

Résultats: 15 cas d'AVC de pédiatrie ont été identifiés, sur un total de 416 enfants inscrits avec 5 CA, donnant un taux de prévalence de la course de 3.6%, ration hommes: femmes était de 1:1. Tous Les Cas d'AVC étaient de l'électrophorèse de l'hémoglobine SS; avec un âge moyen an moment du diagnostic de SCA de 2.2 (1.5) ans et l'âge moyen an début de l'AVC de 6.3 (2.8) ans. Moment de la présentation de l'hôpital après le début de le course était de 10 (2.5) jours. Hémiparésies et l'aphasie expressives sont les Caractéristiques prédominantes. Basé sur les résultants de la neuro-imagerie, la majorité des types d'AVCétaient infinitive 71.4%. Aucune mortalité n'a été enregistrée.

Conclusion: La Prévalence de la faucille connexes aux cellules course d'enfance de 3.6% dans cette série est relativement faible. Majorité des patients se sont présentes à l'hôpital très tard, aprèsle début de la course. Il est donc nécessaire d'avoir la sensibilisation accrue sur les AVC de l'entracte dans notre communauté, afin de faciliter la presentation début de l'hôpital et prise enchante rapide pour améliorer les résultants.

Mots Clés: Course de pédiatrie, la drépanocytose résultanteprésentation tardive, résultants.

* Auteur correspondant: Dr Ahmad Muhammad Murtala, E-mail: murisbn@yahoo.com

Department of Paediatrics, Usmanu Danfodiyo University Teaching Hospital Sokoto, Nigeria

INTRODUCTION

Stroke generally occurs in children more often than previously suspected, with its attendant potential consequences (1, 2) including persistent hemiparesis, dysphasia, seizures or cognitive disturbances, depending on the brain vasculature involved. It is often an under recognized cause of neurologic disability in children, with varied causes and treatment approaches (3). The current definition (21st century) explains stroke as a sudden neurologic disturbance caused by a focal (and not global) cerebral, spinal cord or retinal infarction attributable to ischaemic or non-traumatic haemorrhage within the brain or the ventricular system in a defined vascular distribution, based on clinical, pathologic or imaging findings with symptoms lasting $\geq$24 hours or leading to death, with exclusion of other causes (4).

Mechanisms and risk factors for stroke differ between children and adults (5, 6). Major predisposing factors for childhood stroke includes haemoglobinopathies, heart diseases, haematologic/clotting disorders, cerebral arteriopathies, cerebral sino-venous thrombosis and Central Nervous System (CNS) infections (3). Children with sickle cell haemoglobinopathies have increased risk for stroke (7-9) and up to 12% of them may develop stroke by 21 years (10). Nigerian children with SCA have particularly been shown to have higher transcranial Doppler (TCD) abnormal velocities compared to African-American children (11), hence higher risks of developing a stroke.

Hospital based prevalence of sickle cell anaemia in the study area was reported to be between 4.8 to 11.3% with a carrier rate of 23.3% (12,13). Acute neurologic symptoms may manifest either spontaneously or following an acute illness (14). The prevalence of stroke among Nigerian sickle cell patients was reported to be 12.4 per 1000 for both children and adults, and 7.4 per 1000 for children (15). Unlike other SCA related complications that commonly follow microvascular occlusions, stroke is mainly associated with large vessel vasculopathy (16).

Early restoration of blood flow before tissue death occurs is the basis for prompt intervention required in stroke management. However, despite continuous improvement in the management of many complications of SCA, neurologic complications remain a significant problem (8). There is paucity of information on childhood stroke, particularly among SCA patients in our environment. Therefore, this study aims to determine the pattern of stroke among children with SCA in Sokoto and to the best of our knowledge it is the first of its kind from this area.

METHODOLOGY

Involves a review of all the clinical records of all SCA children (aged 0 to 15 years) diagnosed with stroke and managed in the Department of Paediatrics, Usmanu Danfodiyo University Teaching Hospital, Sokoto, over a ten-year period (May, 2004-April 2014) was undertaken. Manual sorting of the files was done to extract relevant information like age, gender, number of blood transfusion, age at presentation with stroke, mean packed cell volume (PCV), computed tomography (CT) scan reports, treatment and outcome. Data analysis was done using the statistical package for social sciences (SPSS) version 20. Ethical approval was given by the UDUTH Ethics Committee.

RESULTS

Fifteen cases of Paediatrics stroke were identified, out of a total of 416 registered children with SCD, giving a stroke prevalence of 3.6%. All the stroke cases were of haemoglobin SS electrophoresis. Male to Female ratio was 1:1 and mean age at diagnosis of SCA of 2.2 (±1.5) years (range of 7months to 8 years). The mean age of stroke occurrence was 6.3 (±2.8) years with those aged 4 to 6 years constituting 60% of

the cases. Age specific prevalence of stroke were 1.6% (2/125) for Under-five SCA patients and 6.3% (13/208) for those aged five to 10 years. None of the cases developed the stroke from 10 years of age or beyond. Table 1 summarizes some relevant clinical parameters of the children with SCA stroke.

Mean time of hospital presentation after occurrence of the stroke was 10 (±2.5) days (range 8hrs to 28days). This was estimated from the time onset of the initial presenting symptoms of stroke. The mean pre-morbid steady state PCV was 21.5 (±2.5) %, with up to 60% of the patients having received two or more blood transfusions (range of 1-4 times) prior to the stroke onset. Two (13.3%) patients had a secondary (repeat) stroke among the reviewed cases.

Common presenting features identified include hemiparesis (100%), expressive/motor aphasia (20%), cranial nerve palsies (13.3%) and seizures (6.7%). None of the patients presented with coma. Brain imaging was done in only 7 (46.7%) cases. Based on the neuroimaging findings, the stroke types identified were due to cerebral infarction in 71.4% and 14.3% were due to intracerebral haemorrhage. No case of subarachnoid haemorrhage was found. Diffuse cerebral atrophy was demonstrated in 14.3% of the cases, as shown in Table 2.

Treatments given at presentation ranged from exchange blood transfusion (33.3%), initiation of hyper transfusion program (73.3%) to use of hydroxyurea therapy (40%) at 15-30mg per kg, depending on the timing of Hospital presentation and overall clinical condition of the patients. Patients with repeat stroke were commenced on hydroxyurea treatment as secondary stroke prevention. None of the patients had antiplatelets therapy but all patients had physiotherapy.

Up to 26.7% still have some residual motor deficits (mainly hemiparesis) with persistent afebrile seizures in one patient (6.7%). There was no mortality recorded but 26.7% of the patients were lost to follow-up as at the time of this write up.

DISCUSSION

This study showed the prevalence of sickle cell anaemia related stroke to be 3.6%. This figure is lower than that of a similar recent report of 5.2% among children with SCA in Abuja (17). The lower rate in our study may perhaps be explained by genetic and environmental differences between the study groups as well as the likelihood of more hospital presentation after the stroke onset among the Abuja cohort. Late hospital presentation after the stroke onset was alarmingly noted in our study cohort with majority presenting after the first week of stroke occurrence. In more than half of the cases, the delay was attributable to time spent on unorthodox care.

The mean age of stroke occurrence found in this study cohort agrees with earlier reported age of below 10years by some previous studies (17, 18). Low steady state PCV was demonstrated in most of the stroke patients in this study. This conforms to the finding that low haemoglobin is a risk factor for SCA related stroke (10). Therefore, intensive blood transfusion regimen has been demonstrated to reduce the chances of developing a stroke by optimizing haemoglobin level and suppressing the haemoglobin-S level to <30% (10, 19, 20).

Although none of our subjects had transcranial Doppler (TCD) studies to predict the risk of developing a stroke, elevated cerebral blood-flow velocity (using TCD studies) in SCD patients may be related to severe anemia and cerebral vasodilatation caused by cerebral tissue hypoxia. Thus, blood transfusion reduces cerebral blood flow velocities by reversing these abnormalities; with subsequent protection against repeat strokes (21-23). Nigerian children with haemoglobin SS disease have been reported to have higher abnormal TCD

velocities compared to African-American children (11), hence higher risks of developing a stroke. Hankins et al. (24) have also reported 10% of sickle cell children screened by the TCD to have abnormal velocities in the United States.

Elevated white blood cell count is also reported to be another risk factor for stroke in SCA (10). However, the steady state leukocyte levels were not analyzed in this study due to lack of adequate record on such parameters during steady state periods. This underscores the importance of adequate and appropriate patient investigation as well as proper documentation of relevant records during the follow up periods. Despite the availability of neuroimaging techniques in our center, which at least helps to confirm and to determine the stroke subtypes, less than fifty percent of the stroke patients in this cohort were able to do this important diagnostic test, partly due to poverty.

No case fatality was recorded in this study, which may be attributable to the fact that; those patients that would have died early after the stroke may not have reached the Hospital, as the earliest timing of hospital presentation following stroke was 8 hours. However, documented stroke case fatality rates among SCD children varied, with male sex, black race and repeat stroke (s) increasing the chances of death (3).

About one quarter of the patients in this study had residual motor deficits (hemiparesis). This is lower than some earlier reports where more than half of the surviving children were reported to have long-term neurological sequelae, most commonly hemiparesis or hemiplegia (3, 25). However, the very limited number of subjects in our study will hinder a conclusive deduction to be made. Therefore, long term follow-up of identified cases of stroke is essential; especially during the first year following a stroke (25).

Primary stroke prevention in SCA patients is most important because even a single stroke can lead to irreversible brain injury. Transcranial Doppler is a simple, inexpensive and noninvasive means of monitoring cerebral blood flow changes and may aid in making therapeutic decisions regarding transfusion for stroke prevention in children with SCA (26). Thus, the current guidelines in the United Kingdom recommend annual TCD screening of children with SCA from 3years, though some studies have reported a peak incidence of sickle cell stroke starting from 2 to 5 years (18). Also, hydroxyurea therapy has been indicated to significantly decrease elevated TCD flow velocities with ultimate benefit in stroke prevention in children with SCA (27).

CONCLUSION

The prevalence of sickle cell related childhood stroke of 3.6% in this series is relatively low. Majority of the patients presented to hospital very late after the stroke onset. There is therefore the need for increased awareness on childhood stroke in our community, in order to facilitate early hospital presentation and prompt effective management to improve the outcome.

RECOMMENDATION

Sickle cell anaemia is a common problem in Nigeria, though completely preventable through public health education, pre-marital counselling and screening of prospective couples. Primary prevention of stroke in SCA is most important because even a single stroke episode can lead to irreversible brain damage. The use of TCD screening of patients should be made widely available, to aid early identification of at risk children.

REFERENCES

1. Rafay MF. Paediatric stroke management guidelines. J Pak Med Assoc 2010; 60(3):161-2
2. Roach ES, deVeber G, Riela AR, Wiznitzer M. Recognition and

treatment of stroke in children. Child Neurology Society Ad Hoc Committee on stroke in children 2011. www.ninds.nih.gov/news_and_events/proceedings/stroke_proceedings/childneurology.htm

3. Ciceri EF, Cuccarini V, Chiapparini L, Saletti V, Valvassori L. Paediatric stroke: Review of literature and possible treatment options, including endovascular approach. Stroke research and treatment 2011. Doi: 10.4061/2001/781612. Accessed 11th May, 2014
4. Sacco RL, Kasner SE, Broderik JP, Caplan LR, Connors JJ, Culebras A. et al. An updated definition of stroke for the 21st century: A statement for the health care professionals from American Heart Association/American Stroke Association. Stroke 2013; 44:2064-89
5. Long B, Anderson V, Jacobs R, Mackay M, Leventer R, Barnes C et al. Executive function following child stroke: The impact of lesion size. Developmental Neuropsychology 2011; 36(8):971-87
6. Schechter T, Kirton A, Laughlin S, Pontigon AM, Finkelstein Y, MacGregor D et al. Safety of anticoagulants in children with arterial ischaemic stroke. Blood 2012;119:949-56
7. Adams RJ. Big stroke in small persons. Arch Neurol 2007;64(11):1567-74
8. Mahapatra S, Mahapatra S, Sethy S, Das R, Mohanty P and Hazra K. Basal Ganglia Infarct in an Infant with Sickle Cell Disease – A Rare Association. J Blood Disorders Transf 2012; 3(4):125-8
9. Luis A, Verduzco LA, David G, Nathan DG. Sickle cell disease and stroke. Blood 2009; 114:5117-25
10. Balkaran B, Char G, Morris JS, Thomas PW, Serjeant BE, Serjeant GR. Stroke in a cohort of patients with homozygous sicle cell disease. J Pediatr 1992; 120:360-6
11. Lagunju IO, Sodeinde O, Telfer P. Prevalence of cranial Doppler abnormalities in Nigerian children with sickle cell disease. Am J Hematol 2012; 87(5):544-7
12. Abdulrahman Y, Isaac ZI, Erhabor O, Sanusi BM, Udomah F, Ezimah AC, et al. Haemoglobin electrophoretic pattern among residents in Sokoto, Nigeria. Journal of Medical Disorders 2013. Available at http://www.hoajoneline.com/journals. Accessed on 28th November, 2014
13. Umar RA, Hassan SW, Ladan MJ, Matazu IK, Jiya MN and Usman HO. The human genome and malaria: Prevalence of inherited haemoglobin disordres in Sokoto, Nigeria. Intl J Biol Chem 2007;1(3):168-73
14. Khirkham FJ, deBaun MR. Stroke in children with sickle cell disease. Current treatment options in Neurology 2004; 6:357-75
15. Jude MA, Aliyu GN, Nalado AM, Garba KU, Fawodu FO, Hassan A et al. Stroke prevalence among sickle cell disease patients in Nigeria: a multi-center study. Afr Health Sci. 2014;14(2):446-52
16. Adams RJ, Stroke prevention and treatment in sickle cell disease. Arch Neurol 2001; 58:565-8
17. Oniyangi O, Ahmed P, Otuneye OT, Okon J, Aikhionbare HA Olatunji OO et al. Strokes in children with sickle cell disease at the National Hospital Abuja, Nigeria. Niger J Paed 2013; 40(2):158-64
18. NHS Sickle and thalassemia screening program. Sickle cell disease in childhood: Standards and guidelines for clinical care. Available at http://www.sickleandthal.org.uk/Documents/ProgrammeSTAN.pdf.

Accessed 11th May, 2012.
19. Forsyth R and Newton R. Stroke. In: Forsyth R and Newton R (Eds.) Oxford specialist hand book in Paediatrics, Paediatric Neurology 2nd Edition, Oxford university press 2012; 446-51
20. Abboud MR, Yim EY, Musallam KM, and Adams RJ. Discontinuing prophylactic transfusions increases the risk of silent brain infarction in children with sickle cell disease: data from STOP II. Blood 2011;118(4):894-8
21. Russell MO, Goldberg HI, Hodson A. Effect of transfusion therapy on arteriographic abnormalities and on recurrence of stroke in sickle cell disease. Blood 1984;63:162-9
22. Powers D, Wilson B, Imbus C, Pegelow C, Allen J. The natural history of stroke in sickle cell disease. Am J Med 1978;65:461-71
23. Pegelow CH, Adams RJ, McKie V, Abboud M, Berman B, Miller ST et al. Risk of recurrent stroke in patients with sickle cell disease treated with erythrocyte transfusion. J Pediatr 1995;126:896-9
24. Hankins JS, Fortner GL, McCarville MB, Smeltzer MP, Wang WC et al. The natural history of conditional transcranial Doppler flow velocities in children with sickle cell anemia. British Journal of Haematology 2008;142:94-9
25. Roach ES, Golomb MR, Adams R, Biller J, Daniels S, Deveber G et al. Management of strike in infants and children: A scientific statement from a special writing group of the American Heart Association stroke council and the council on cardiovascular disease in the young. Stroke 2008;39:2644-91
26. Lee MT, Piomelli S, Granger S et al. Stroke prevention trial in sickle cell anaemia (STOP): extended follow-up and final results. Blood 2006; 108(3):847-52
27. Zimmerman SA, Schultz WH, Burgett S, Mortier NA and Ware RE. Hydroxyurea therapy lowers transcranial Doppler flow velocities in children with sickle cell anaemia. Blood 2007;110(3):1043-1047

Table 1: Details of the clinical parameters of the children with sickle cell stroke

S/No	Gender	Current age (year)	Age at diagnosis of SCA (year)	Age at time of stroke (year)	Mean steady state PCV (%)
1.	F	6	3	6	17
2.	M	6	1.3	4	25
3.	F	6	3	6	20
4.	F	7.5	0.92	5	22
5.	M	8	8	8	25
6.	M	8	0.58	7	20
7.	F	9*	0.58	5	20
8.	M	12	1.3	8.5	21
9.	F	12	0.75	9	18
10.	M	13	1	9	23
11.	F	15*	2.5	6	24
12.	F	4.5	0.83	4	21
13.	M	9	3	7	22
14.	F	8	2.5	5	21
15.	M	9	3	5.5	23

SCA= sickle cell anaemia; Hb=haemoglobin; PCV= packed cell volume; *repeat stroke

Table 2: Neuroimaging findings of the 7 patients that had the test

Cases	**Gender**	**Age at stroke (yr)**	**Brain imaging findings**
1	M	6	Left cerebral infarction
2	F	7	Right cerebral Infarction
3	M	9	Left cerebral infarction
4	F	6	Left cerebral infarction
5	F	5	Diffuse cerebral atrophy
6	F	5	Right intracerebral haemorrhage
7	F	9	Right cerebral infarction