Stroke Prevalence in Children With Sickle Cell Disease in Sub-Saharan Africa: A Systematic Review and Meta-Analysis

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Abstract
Objectives. The prevalence of stroke among children with sickle cell disease (SCD) in sub-Saharan Africa was systematically reviewed. Methods. Comprehensive searches of PubMed, Embase, and Web of Science were performed for articles published between 1980 and 2016 (English or French) reporting stroke prevalence. Using preselected inclusion criteria, titles and abstracts were screened and full-text articles were reviewed. Results. Ten full-text articles met selection criteria. Cross-sectional clinic-based data reported 2.9% to 16.9% stroke prevalence among children with SCD. Using available sickle gene frequencies by country, estimated pediatric mortality, and fixed- and random-effects model, the number of affected individuals is projected as 29 800 (95% confidence interval = 25 571-34 027) and 59 732 (37 004-82 460), respectively. Conclusion. Systematic review enabled the estimation of the number of children with SCD stroke in sub-Saharan Africa. High disease mortality, inaccurate diagnosis, and regional variability of risk hamper more precise estimates. Adopting standardized stroke assessments may provide more accurate determination of numbers affected to inform preventive interventions.

Keywords
sickle cell disease, stroke, sub-Saharan Africa, systematic review

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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 Worldwide, an estimated 300 000 children are born with SCD annually; 80% in SSA.3 Although precise data are lacking, under-5 mortality from SCD in SSA has been estimated at 50% to 90%.4 SCD is the most common cause of pediatric stroke. Children with the most severe and prevalent sickle type, homozygous S disease (HbSS), have the highest risk.5 SCD brain vasculopathy causes both overt stroke and “silent” cerebral infarcts, affecting neurological and cognitive function.6 Prior to systematic screening and intervention, HbSS-associated pediatric stroke prevalence in the United States and France was 11%.5,7 Highest risk of first overt ischemic stroke is within the first decade of life.7 Strokes continue to accumulate through childhood.8 Consequences of pediatric SCD stroke include mortality and long-term impaired function and development.

SCD cerebral vasculopathy is mediated by defects in vascular hemodynamics, hemolysis-associated oxidative stress, hemostatic activation, and cellular adhesion.7 Pediatric SCD stroke often follows within days of acute inflammatory disease manifestations such as pain crises.
and acute chest syndrome. Low steady-state hemoglobin and acute severe anemia have also been shown to increase stroke risk in patients with SCD and certain genetic variants. It is unknown whether the prevalence of overt SCD stroke in SSA differs from that seen in high-income countries. The setting in SSA of a high burden of infection and malnutrition, challenges for provision of standardized care, and variation in genetic background may predispose children with SCD to regional differences in disease complications. In this article, we systematically review the published literature on the prevalence of overt stroke in pediatric SCD by country in SSA and estimate the region’s total affected population. Understanding the number of children affected by SCD stroke is critical for focusing public health efforts to introduce preventive measures to reduce stroke risk and to implement rehabilitative strategies. A recent study reviewing neurologic complications of SCD in Africa highlights the interest in this area of research.

Materials and Methods

This review is reported according to the guidelines outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement. We performed a systematic search for all studies reporting prevalence data of stroke in pediatric patients with SCD published between 1980 and December 13, 2016, in English or French. Searches were performed using PubMed (www.ncbi.nlm.nih.gov/pubmed), EMBASE (www.scopus.com), and Web of Knowledge (www.webofscience.com). The primary search included appropriate keywords and accepted MeSH terms or terms in the title/abstract: “anemia, sickle cell” OR “sickle cell disease” OR “HbS disease” AND “brain” OR “stroke” OR “cerebrovascular accident” OR “cerebrovascular ischemia” OR “cerebral ischemia” OR “brain ischemia” OR “brain diseases” AND “Africa South of the Sahara” OR “Sub-Saharan Africa” OR “Sub-Saharan Africa” OR each country within SSA. Titles and abstracts of all identified eligible articles were screened by LJM. Full-text articles were reviewed by LJM and NSG, with NSG providing final review of articles in French. Records were excluded if they were not based in Africa, not specific for stroke, not specific for SCD, or were abstracts only. Additionally, full-text articles were excluded if they were review articles, were solely based on a questionnaire, were case reports, presented adult-only data, were treatment related, lacked cross-sectional data, lacked a clear definition of stroke criteria, or contained possibly overlapping data as this could bias reported prevalence. Data from all articles fitting inclusion criteria have been cited.

Information extracted from each study was the following: type of study, description of clinic location and characterization, study dates, stroke definition, sample size, stroke prevalence, how sickle cell diagnosis was confirmed, whether imaging was performed, what treatment if any was given, and stroke recurrence if reported. Data from the included studies were independently extracted in duplicate by LJM and NSG using a standardized electronic form (Microsoft Excel). Disagreements in article selection or information extracted were discussed to reach agreement. Key relevant articles were selected for providing background information.

Results

In total, 162 records were identified through the database search and through the review process (Figure 1). After duplicates were removed and after 4 were removed due to publication prior to 1980, 133 individual articles remained. These 133 titles and abstracts were screened by LJM. Of these, 62 were excluded either due to being studies not based in SSA (n = 20), not specific for stroke (n = 21), not specifically involving SCD (n = 10), or consisting only of an abstract (n = 11). In all, 71 full-text articles were assessed, including 66 in English and 5 in French. Of these, further exclusions were made due to articles being the following: reviews (n = 33), questionnaires (n = 2), case reports or case series (n = 6), pertaining to SCD treatment (n = 12), lacking cross-sectional prevalence data (n = 5), or possible overlap of data with another report from the same site (n = 1). Data from all 10 articles fitting inclusion criteria have been cited, including one in French. In all, articles reported data from 7 countries in the region, including 4 reports from Nigeria.

Stroke prevalence has been published for only a few of the region’s countries, all of which are described below and shown in Table 1. Geographical distribution of the studies across SSA is shown in the map in Figure 2. In each country, stroke prevalence data were obtained from cross-sectional SCD clinic samples or retrospective review of hospital admissions. Strokes were diagnosed by patient examination and/or medical history of an acute neurological event consistent with a stroke. Limited data on brain imaging were provided; most reports stated that brain imaging was not available. None of the articles included details of the process used for adjudicating events or effects.

By Country

Reports from 7 different countries in SSA met inclusion criteria for systematic review (Table 1).
Cameroon

In one study reported from 2 SCD clinics in Yaoundé, 120 patients with a mean age of 13.5 ± 8.8 years presenting to clinic over a 3-month period were screened for history of an acute stroke. Eight patients (6.7%) were identified with a history of stroke, and 5 of 8 patients with stroke had computed tomography scans, all of which confirmed the diagnosis. Two patients with recurrent stroke had been treated with aspirin for secondary prophylaxis, neither received hydroxyurea nor chronic transfusion therapy.

Congo

Of 1422 children with HbSS admitted to the Brazzaville Teaching Hospital in the capital city of Brazzaville, 15 (1.1%) were diagnosed with a stroke. Over half of these children with stroke were 5 to 10 years of age and most presented with hemiplegia. Several of the patients had concurrent fever, severe anemia, or dehydration and new onset of seizures. This study suggests that acute febrile illnesses, especially if associated with severe anemia, are risk factors for stroke in SCD.

Kenya

A retrospective review of 360 children aged 0.6 to 21 years (mean age 11.1 ± 6 years) with SCD followed at Kenyatta National Hospital in Nairobi found 12 (3.3%) with history of stroke. An additional 6 patients with other neurologic disorders, including seizures, were considered as having other neurologic conditions.

Malawi

A cohort of children at Kamuzu Central Hospital in the capital city of Lilongwe were screened and confirmed for HbSS. Of the sample of 117 (median age was 7.3 years [interquartile range = 2.7-10.4]), 10 (8.5%) had a history of stroke.
| Country          | Method(s) Used                  | Study Site                          | Study Dates          | Sample Size | Sample Age (Range) | Clinical Stroke Criteria                                      | Imaging | Number With Stroke (%) | Reference |
|------------------|--------------------------------|-------------------------------------|----------------------|-------------|--------------------|--------------------------------------------------------------|---------|------------------------|-----------|
| Cameroon         | Descriptive cross-sectional study | Central Hospital and Mwoye Catholic Centre, Yaounde | October to December 2003 | 120         | 13.5 ± 8.8 (0.6-35) years | WHO definition<sup>a</sup>                                      | 5/8 patients had CT scan, all of which confirmed diagnosis | 8 (6.7%) | 15                     |
| Republic of the Congo | Retrospective chart review of hospital admissions | Brazzaville Teaching Hospital, Brazzaville | May 1995 to May 2002 | 1422        | 0.5-17 years       | Motor deficit, loss of consciousness, or prolonged seizure, excluding febrile seizure, without other detectable etiology | None    | 15 (1.1%)              | 16        |
| Kenya            | Retrospective chart review of hospital admissions | Kenyatta National Hospital, Nairobi | January 1983 to January 1988 | 360         | 10.8 ± 8 (0.6-21) years | Presence of hemiplegia with severe neurologic deficit | No CT scans of initial event | 12 (3.3%) | 17                     |
| Malawi           | Descriptive cross-sectional study | Kamuzu Central Hospital, Lilongwe University College Hospital, Ibadan | January to May 2015 | 117         | 7.3 years (2-10)    | Patient reported history of stroke                           | None    | 10 (8.5%)              | 18        |
| Nigeria          | Retrospective chart review of hospital admissions | Lagos University Teaching Hospital, Lagos | July 2004 to June 2005 | 322         | <16                | Acute onset of focal brain dysfunction manifested as hemiplegia and/or cranial nerve palsies | 7 patients had confirmatory CT scans (5 with infarcts, 2 with hemorrhage) | 27 (5.4%) | 20                     |
| Nigeria          | Case-control study using questionnaire in clinic patients | University College Hospital, Ibadan | July 2009 to June 2011 | 187 HbSS; 27 HbSC | 8.8 (1-16) years including patients with HbSC | WHO definition<sup>a</sup>                                      | All patients with clinical signs of stroke had CT scan performed confirming diagnosis | 17 (9.1%) | HbSS: 1 (3.7%) HbSC    |
| Nigeria          | Descriptive cross-sectional study | Obafemi Awolowo University Teaching Hospital, Ilesa | January to December 2013 | 217 HbSS (90.6%); 23 HbSC | 6 (0.5-15) years, including patients with HbSC | Acute neurologic symptoms/signs secondary to occlusion of and/or hemorrhage from cerebral vessels | The 4 patients presenting with clinical acute stroke all had confirmed infarcts by CT or MRI | 7 (2.9%) | 23                     |
| Tanzania         | Descriptive cross-sectional study | Bugando Medical Centre, Bugando | August to September 2012 | 124         | 6 (1-15) years     | Acute focal neurological deficit in a pattern consistent with stroke syndrome | Not reported | 21 (169%)              | 24        |
| Uganda           | Retrospective cross-sectional study | Mulago Hospital, Kampala | August 2012 to August 2014 | 2870        | 5 (0.5-17) years   | WHO definition<sup>a</sup>                                      | Not reported | 178 (6.2%)             | 25        |

Abbreviations: WHO, World Health Organization; CT, computed tomography; HbSS, homozygous S disease; HbSC, heterozygous for hemoglobin C and S disease; MRI, magnetic resonance imaging.

<sup>a</sup>WHO Stroke Definition: Rapidly developing clinical signs of focal (or global) disturbance of cerebral function, with symptoms lasting 24 hours or longer or leading to death with no apparent cause other than of vascular origin.
Nigeria

Nigeria has the world’s largest SCD population, reflecting the large population and high national prevalence of S trait. Consequently, the country is especially burdened by the large number of children with SCD stroke. Based on several clinic-based assessments of children with SCD mentioned in this article, estimates of stroke prevalence in Nigeria range from 2.9% to 8.6%. A retrospective study from the University of Ibadan found that, out of 500 children ≤16 years with SCD, 27 (5.4%) had a history of stroke, 7 with confirmatory computed tomography scans. Mean age of first stroke was 6.8 years (range = 17 months to 11 years). Recurrent stroke occurred after an average time of 25.6 months in 8 of 13 patients (61.5%) followed. Among 322 patients evaluated at the outpatient SCD clinic at the University of Lagos, stroke prevalence was 6 of 96 (6.3%) for children aged 4 to 14 years (mean 9.9 years) and 11 of 226 (4.9%) for adolescents aged 15 to 19 years (mean 18.1 years).

A cross-sectional study of 240 pediatric patients with SCD, mean age 6 years (range = 0.5-15), seen at another teaching hospital in Southwestern Nigeria for SCD follow-up or emergency care over the course of a year, 7 (2.9%) had suffered a stroke.

Tanzania

Tanzania is reported to have a high birth prevalence of SCD. A cross-sectional study carried out at the Bugando Medical Centre in Mwanza evaluated complications of SCD in a sample of 124 patients aged from 1 to 15 years, with a median age of 6. Of these, 21 (16.9%) had a history of stroke. Diagnosis of prior stroke was made solely in children aged 6 years or older, with over 40% of those older than 9 years. By multivariate logistic regression, 2 risk factors were identified: older age and a younger age at diagnosis of SCD.

Uganda

In a retrospective study from Mulago Hospital in Uganda, medical records were evaluated for 2870 children with SCD, aged 6 months to 17 years, admitted over a 2-year period. Stroke prevalence was found to be 6.2%. Of those diagnosed with stroke, many had
comorbidities including severe anemia (30%), bacteremia (21%), or vaso-occlusive crises (24%).

Additional Data From Other Countries in SSA

Several published reports from other African countries on pediatric SCD and stroke did not meet selection criteria. These data are mentioned here as illustrative of regional variation in stroke prevalence but were not included in the systematic review. One report from Benin of a SCD sample of 34 SCD patients found that 12 (35%) had neurologic deficits believed to be secondary to stroke.26 However, this study only assessed and reported on patients in rehabilitation, and as such, it was enriched for neurological disease and did not represent a cross section of SCD patients. A retrospective review of 307 pediatric patients with HbSS in Senegal had a low stroke prevalence with only 4 cases (1.3%).27 Similarly, a retrospective study in South Africa reported one patient with stroke of a sample of 58 SCD patients (1.7%).28 Last, a case series from Kenya without prevalence data reported 6 pediatric patients with SCD and neurological complications presumed to be from stroke.29

Approximate Pediatric SCD Stroke Burden

Estimates of number of neonates born with HbSS by Piel et al by country1 provide data to calculate the estimated number of children with SCD in SSA. Estimated prevalence of HbSS among infants in Uganda, 1 of the 7 countries for which evidence is considered, is supported by a recent national assessment of archived samples.30 Specifically, we used the total number of neonates born per year with HbSS in SSA and multiplied by 18 years to estimate total number of children. Using the published estimate of under-5 mortality of children with SCD in SSA of 50% to 90% by Grosse et al,4 we assumed an overall pediatric mortality of 75%. Based on this estimate, we calculate that approximately 1.027 million children aged 0 to 18 years in SSA have HbSS.

Significant heterogeneity was found between the 10 studies included here (Cochrane’s $Q$-statistic = 143.8, degrees of freedom = 9, $P = .001$) and $I^2$-statistic = 94.4% (95% confidence interval [CI] = 91.4% to 96.4%). The pooled estimate of the stroke prevalence was 2.90% (95% CI = 2.49% to 3.31%) based on fixed-effect analysis and 5.82% (95% CI = 3.60% to 8.03%) based on random-effect analysis.31 Applying the pediatric stroke prevalence of 2.9% to 16.9% from the systematic review and using a fixed- and random-effects model, pediatric stroke prevalence in SSA was projected as 29 800 (95% CI = 25 571-34 027) and 59 732 (37 004-82 460), respectively. Nigerians account for approximately 48% of those affected by SCD and SCD stroke in SSA.

Discussion

SCD in SSA is associated with high mortality and major medical and social burdens. Worldwide, SCD is the most common cause of pediatric stroke.3 To focus on the serious complication of SCD stroke in the region, we systematically reviewed existing data on its prevalence in children. Data from clinic-based cross-sectional samples in 7 countries were available. In total, these data are within a 2- to 3-fold prevalence of pediatric SCD stroke in the United States prior to institution of standardized stroke prevention strategies.3 Using these data and an estimate of the total number of children with SCD in SSA based on existing reports,1,4 we generated an estimate of the prevalence and the number of children affected by SCD stroke in SSA. This review approximates the upper and lower boundaries of pediatric SCD stroke prevalence in SSA. Given the potential for variability in stroke prevalence between study samples and countries studied, we favor the upper boundary generated by the random-effects model. Our findings suggest that approximately 60 000 children in SSA have strokes related to SCD.

Our estimate of stroke prevalence is similar to that reported in a recent review of SCD stroke combining children and adults across Africa.12 Similar to our findings, they also reported a higher stroke prevalence in studies utilizing diagnostic imaging and clear diagnostic criteria. Our systematic review and meta-analysis summarize what is known about pediatric SCD stroke in SSA. Accuracy is limited by the small number of published reports of varying rigor, clinic-based samples, and other potential biases. Our analysis also highlights the gaps in knowledge, including SCD population size and structure in each country, imaging and other diagnostic tools, and uniform diagnostic criteria. Additional gaps in knowledge include rates of stroke recurrence, long-term complications, and generalizable impact from primary and secondary stroke prevention.9,13

High disease- and stroke-related mortality are expected to lead to underestimation of children affected by stroke in SSA in 2 ways: (1) in the absence of newborn screening, high early childhood mortality may reduce the estimated prevalence of SCD in each country4; and (2) poor survival associated with SCD stroke may reduce the observed prevalence of patients affected by stroke in clinic-based studies. Despite these limitations, a large number of children in the regions are affected by stroke and associated adverse health outcomes.

Risk for SCD stroke within SSA may include factors that are more prominent in low-income countries,
especially severe anemia from malaria and other acute or chronic infections, malnutrition, and meningitis. Additional SCD stroke risk in SSA may arise from limited access to routine care, which is generally available in high-income settings, including hydroxyurea therapy and transcranial Doppler screening.

In high-income countries, effective primary prevention for SCD stroke is based on identifying and intervening for children at highest stroke risk. Annual noninvasive screening for high vascular flow through the Circle of Willis using transcranial Doppler ultrasound is standard of care. The mainstay of primary and secondary stroke prevention for those at high stroke risk is through chronic blood transfusion therapy. Extrapolating from these successes to SSA, primary stroke prevention through regular screening followed by chronic transfusion or hydroxyurea therapy for those at highest stroke risk could substantially reduce the stroke burden from SCD in SSA. Efforts for primary prevention in Nigeria are already underway at several sites, demonstrating the feasibility of implementing prevention of primary stroke in the region and possibly stroke recurrence. High economic costs, availability of safe chronic blood transfusions, concerns for blood-borne infections such as HIV, and cultural beliefs represent some of the main challenges in utilizing chronic transfusion. Whether hydroxyurea or another treatment available for SCD stroke prevention will provide more practical preventive measures in resource-poor areas remains to be tested. Assuming the possibility of additional SCD stroke risk factors in the region, the approach to both primary and secondary stroke reduction may need to be adapted accordingly. These other risk factors should be studied and identified to tailor interventions that are appropriate and effective in SSA, presumably in addition to approaches used in high-income countries.

Within most of the SSA, diagnosis of SCD stems from clinical recognition of disease-related complications. Such was the case in all but one of the reports cited in this article. Newborn hemoglobinopathy screening programs have been piloted or adopted in several countries in SSA for early diagnosis and institution of preventive measures. These programs are providing data on the burden and distribution of SCD within individual countries, and they are intended to facilitate the implementation of standardized measures for preventing disease-associated complications.

Limitations to data quality include absence of brain imaging for sensitive and specific stroke diagnoses, including silent infarcts. In some reports cited in this article, other neurologic disorders possibly stemming from stroke (eg, seizures) were considered as strokes. Stroke incidence was not reported, so demographic subsets (eg, peak age range of primary stroke) or precipitating factors could not be determined. SCD stroke impact on child survival, neurologic and neurocognitive function, age of stroke onset, and recurrence are unknown. All of the studies were clinically based and therefore did not include patients with subclinical infarcts and those unable to access care. Available data likely skew toward surviving patients, leading to possible underreporting of people at risk for SCD stroke, especially for the stroke-prone severe phenotype of HbSS. Paucity of population-based data on SCD in the region and high early mortality may bias estimates by reducing identified stroke prevalence. The impact of recurrent stroke was also difficult to assess due to variable follow-up times and limited reporting. Even as we have attempted to restrict reported data to patients with HbSS, the uneven distribution of SCD prevalence and severity across SSA, including a range of haplotypes (eg, from Senegal) and milder genotypes (eg, HbSC), further complicate the estimation of those with SCD stroke across the region.

Garnering essential public health resources for building health care systems to meet the challenge of addressing SCD stroke, both for prevention and treatment, will be supported by documentation of the population burden of disease. Accurate prevalence estimates would facilitate tracking of the impact of public health preventive and therapeutic strategies. Economic and public health advancements in many parts of the region, accompanied by continued expansion of SCD programs of newborn screening and treatment, are predicted to improve survival of affected children in need of appropriate medical services. Analysis of the cost savings from newborn SCD screening and institution of early preventive care in SSA was recently published. The potential for effective stroke diagnosis with brain imaging would improve the specificity of stroke diagnosis. Primary prevention using standardized screening by transcranial Doppler ultrasound and treatment with blood transfusion or perhaps hydroxyurea therapy may reduce its burden among large populations within the region. Given the large number of children estimated with stroke burden in SSA, the likely impact on mortality and development, and the efficacy of prevention in high-income countries, primary SCD stroke prevention should be given high public health priority.

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DM: Contributed to conception; critically revised the manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy.

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NSG: Contributed to conception and design; contributed to acquisition, analysis, and interpretation; drafted the manuscript; critically revised the manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy.

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