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Original Article

Stroke Recurrence in Nigerian Children With Sickle Cell Disease: Evidence for a Secondary Stroke Prevention Trial

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ABSTRACT

Background: To improve the quality of care for children with sickle cell anemia in Kano, Nigeria, we initiated a standard care protocol in 2014 to manage children with strokes at Aminu Kano Teaching Hospital.
Methods: The standard care protocol requires that children with acute strokes be treated with hydroxyurea at a fixed dose of 20 mg/kg/day within two months of the stroke.
Results: Twenty-nine children with sickle cell anemia and initial stroke were identified based on clinical World Health Organization criteria from 2014 to 2017. Follow-up was a median of 1.04 years (interquartile range 0.43 to 1.83 years) to either July 2017 or a second stroke, corresponding to an initial stroke incidence rate of 0.88 per 100 patient-years. Eight children had a recurrent stroke, six of whom were prescribed hydroxyurea 20 mg/kg/day by two months after initial stroke. Two children died. Six of the recurrent strokes occurred within six months of the initial stroke, two before hydroxyurea prescription. The stroke recurrence rate was 17.4 events per 100 patient-years. Adherence was approximately 60%, partly because families had to pay for hydroxyurea. Stroke incidence is probably underestimated because despite formal training for stroke detection during the quality improvement period, no participant had assessment using a standardized pediatric stroke scale and neuroimaging was not available.
Conclusions: In children with sickle cell anemia, a high rate of initial and recurrent strokes exists in a low-resource setting. Ongoing needs include training to detect strokes with an objective stroke assessment and government-supported free access to hydroxyurea for stroke prevention.

Introduction

Each year about 300,000 children are born with sickle cell disease (SCD) worldwide, with nearly two thirds of these births occurring in Africa.[1] In a recent survey, we demonstrated that Kano, a state in northern Nigeria, has the highest number of children with SCD in Nigeria, with Murtala Muhammad Specialist Hospital in Kano having about 10,000 children registered at the pediatric SCD clinic.[2] In contrast to high-income countries, SCD-related childhood mortality in sub-Saharan African countries such as Nigeria remains high at 50% to 90%,[3] with fewer than half of the children reaching their fifth birthday.[3]

Stroke is one of the most important causes of mortality in children with SCD.[4] Without transcranial Doppler (TCD) ultrasound screening and regular blood transfusion therapy for those with abnormal TCD measurements, approximately 10% of the children with sickle cell anemia (SCA) defined as phenotype hemoglobin (Hb) SS or HbSβ^0 thalassemia, not screened for abnormal TCD measurements nor treated with regular blood transfusion therapy, will develop strokes. Among untreated children with strokes, at least 50% experience a second stroke after two years,[4] with a mortality rate of 20% to 30%.[4] Because of this high rate of stroke recurrence and the absence of regular blood transfusion therapy as

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an option in Nigeria because of poor availability of blood, poor parental acceptance of blood transfusion, and cost, hydroxyurea is the only viable treatment option for most children.[5]

Preliminary data supporting the potential use of hydroxyurea therapy for secondary stroke prevention in children with SCD in sub-Saharan Africa are based on a meta-analysis conducted by our team. The expected incidence rates of stroke recurrence when on regular blood transfusion therapy, hydroxyurea therapy, or no therapy were found to be 1.9 (95% confidence interval [CI] 0.1.0 to 2.9), 3.8 (95% CI 1.9 to 5.7), and 29.1 (95% CI 19.2 to 38.9) events per 100 patient-years, respectively.[6] This meta-analysis clearly demonstrates that hydroxyurea therapy is significantly better for secondary stroke prevention than no therapy, which is the current standard of care in most sub-Saharan countries and in the northern Nigeria region. However, the benefits and risks of hydroxyurea therapy for secondary stroke prevention are poorly defined in Nigeria.

Since 2014, based on the evidence that hydroxyurea therapy has some benefit in secondary stroke prevention,[6] the hematology team at Aminu Kano Teaching Hospital (AKTH) in Kano, Nigeria, elected to introduce a uniform strategy for secondary stroke prevention as part of a quality improvement program. We introduced hydroxyurea therapy as standard care for all children with SCA and prior strokes. We report the results of this quality improvement strategy for secondary stroke prevention in a low-resource setting.

Methodology

The study was conducted at the pediatric SCD clinic of AKTH located in Kano, Northern Nigeria. Approximately 1100 children, age birth to 15 years, are seen annually at this pediatric SCD clinic. The clinic runs weekly, with about 80 children seen each clinic day. Approval to conduct the study was received from the ethics committees of AKTH and Vanderbilt University Medical Center. A standard care protocol for secondary stroke prevention was created, reviewed, and initiated for all children with SCA and new strokes from January 2014 through July 2017. As part of our inclusion criteria, we reviewed all medical charts of children with strokes and SCA (HbSS and HbSβ^0 thalassemia) identified through the SCD clinic, and retrieved all eligible files. Of note, stroke was defined according to the World Health Organization criteria as a new focal neurological deficit lasting for greater than 24 hours.[7] Neuroimaging was not routinely available. Data extracted for each child included age at time of first stroke, date of birth, sex, parental income, parental education, weight, height, complete blood count result at first visit and at most recent clinic visit, date of first stroke, number of strokes (defined by the number of clinical events as mentioned previously), side of stroke, any secondary stroke prevention strategy (blood transfusion or hydroxyurea therapy), history of recurrence, number of recurrent strokes, year of each recurrence, side of recurrence, date of last visit, and patient status at the time of review. The modified Rankin Scale[8] (mRS) and the gross motor classification system[9] were scored from the most recent clinic visit between January and July 2017 via parental interview and examination of the child. The mRS was categorized in a standard fashion as either no to slight disability (score of 0 to 2), where a score of 2 or less is considered functional independence, or moderate disability or worse (score of 3 to 6).[10] Hydroxyurea therapy was prescribed on diagnosis of a stroke, a fixed dose of approximately 20 mg/kg/day. All hydroxyurea prescriptions were self-pay because there is no public health insurance to cover the expense of hydroxyurea.

Before initiating the protocol, multiple members of the pediatric care team received training on conducting the Pediatric National Institutes of Health Stroke Scale (PedNIHSS) (https://www.phenxtoolkit.org/toolkit_content/PDF/PX820802.pdf).[7,11] All data were entered into an electronic database and reviewed by a second assistant to ensure accuracy.

Statistical analysis

We summarized study variables using the median and interquartile range (IQR) for continuous data and percentages for categorical data. We assessed stroke prevalence using proportions. We assessed mortality and stroke recurrence using rates and percentages. Comparisons of the pretreatment laboratory values for mean cell volume (MCV) and values at 12 months after starting hydroxyurea therapy for patients on hydroxyurea were conducted to determine the differential change from baseline and thus adherence. A P value <0.05 was considered statistically significant. All analyses were performed with IBM Statistical Package for the Social Sciences (SPSS) Statistics (Version 25).

Results

Demographics

On the basis of the World Health Organization criteria and a standardized neurological examination,[11] a total of 29 children with SCA were diagnosed with a stroke during the sampling frame. The median age at the time of first stroke was 6.0 years (range 1.1 to 14.2 years), with 18 (62.1%) males. The median hemoglobin level at the time of stroke was 8.2 g/dL. After implementing, as standard care in the clinic, a fixed dose of approximately 20 mg/kg/day of hydroxyurea therapy for secondary stroke prevention, 93.1% (27 of 29) of children were started on hydroxyurea therapy within two months of the first stroke.

Nigerian children with SCA experience a high rate of stroke and stroke recurrence

A total of 2.6% (29 of 1100) of children with SCA had an initial stroke within the study period. Twenty-seven percent (eight of 29) of children have at least one recurrent stroke within 3.3 years of the first stroke. The median time to recurrence was 0.35 years with 75% (six of eight) of the recurrences within the first six months (Fig 1), and the earliest stroke recurrence occurring within two months of the first stroke. The rate of initial stroke in the pediatric SCD clinic population (age birth through 15 years) was 0.88 per 100 patient-years (95% CI 0.60 to 1.25 per 100 patient-years) (Fig 2). Children with initial strokes were followed for a total of 36.4 years to the end of follow-up or a second stroke, and had a rate of recurrence of 22.0 events per 100 patient-years (95% CI 10.2 to 41.8 per 100 patient-years). The median follow-up was 1.04 years (IQR 0.43 to 1.83 years). The rate of recurrence for children who followed the protocol of starting hydroxyurea therapy within two months of the initial stroke (27 of 29) was lower, at 17.4 events per 100 patient-years (95% CI 7.1 to 36.3 events per 100 patient-years).

High mortality rate associated with strokes

We recorded two deaths among the 29 children, for an overall mortality rate of 4.0 events per 100 patient-years (95% CI 0.7 to 13.3 events per 100 patient-years). Both children were on hydroxyurea therapy for secondary stroke prevention. The mortality rate for the 27 children on hydroxyurea per protocol was 4.3 events per 100 patient-years (95% CI 0.7 to 14.3 events per 100 patient-years). Death was unrelated to myelosuppression. The first child who died had a stroke at age six years and had three recurrent strokes within two years of the initial stroke, whereas the second child had

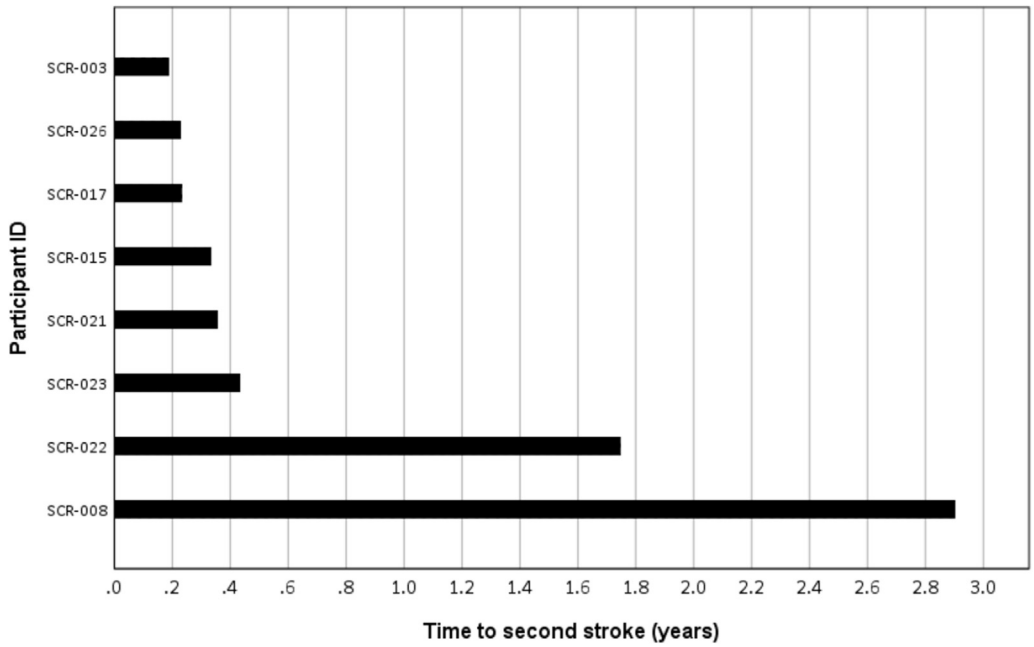

FIGURE 1. Time to second stroke for children with sickle cell disease. The figure shows that 75% of children have stroke recurrence within six months of their first stroke.

one stroke at age 11 years. The mortality rate from first stroke to end point (second stroke, death, or end of study follow-up) was 2.75 events per 100 patient-years (two deaths in 36.4 cumulative patient-years), 95% CI (0.04 to 15.30 per 100 patient-years). The mortality rate from second stroke to end point or death was 7.41 per 100 patient-years (one death in 13.5 cumulative patient-years) with a 95% CI (0.10 to 41.24 per 100 patient-years).

Children receiving fixed moderate dose of hydroxyurea with SCA do not experience increased toxicity associated with hydroxyurea therapy for secondary stroke prevention

Of the 29 children with an initial stroke, 65.5% received an initial exchange transfusion. Transfusion therapy was not continued at regular intervals because of either poor availability of blood, poor parental acceptance of blood transfusion, or cost. For secondary prevention of strokes, 93.1% (27) were either already on hydroxyurea (n = 1) or started on a fixed dose of hydroxyurea (n = 26), 20 mg/kg/day, within two months of the stroke, as part of standard care. None of the children treated with hydroxyurea had therapy held because of myelosuppression or anemia.

Adherence to hydroxyurea therapy for secondary prevention of strokes was assessed via increase in MCV in 21 of the 27 children who began hydroxyurea within two months. The other six children had missing values for MCV because of incomplete complete blood count records. As an indirect measure of adherence, 61.9% (13/21) of patients had an increase in MCV by at least 10.0 femtoliters (fL), with the mean MCV increasing from 86.2 fL at baseline to 101.3 fL at 24 months. Mean last MCV was 111.3 and 98.2 fL in those with and without recurrence, respectively ($P = 0.035$). However, adherence

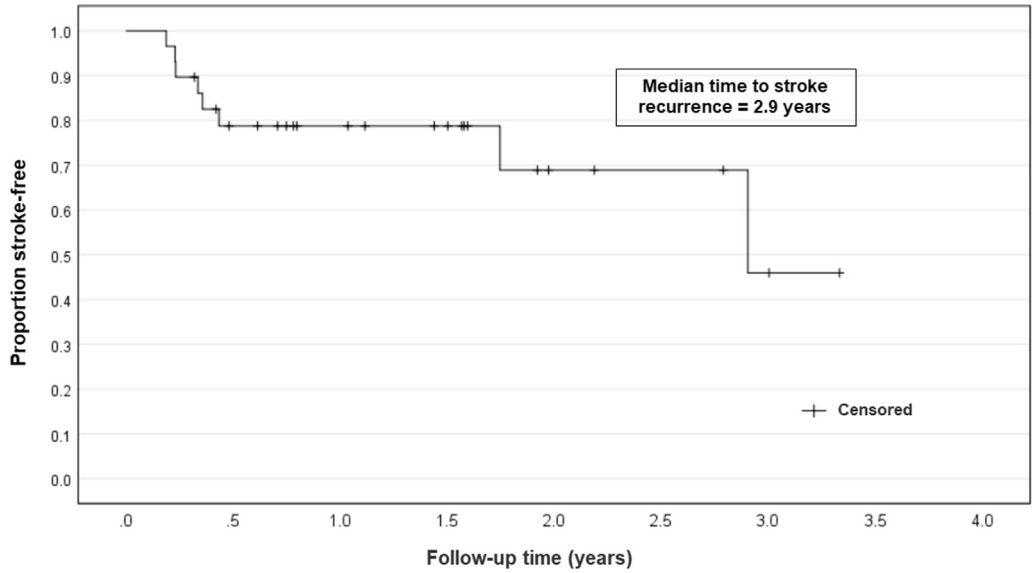

FIGURE 2. Kaplan-Meier plot of time to stroke recurrence after first stroke (n = 29). The plot shows the median survival time after stroke recurrence, which was 2.9 years.

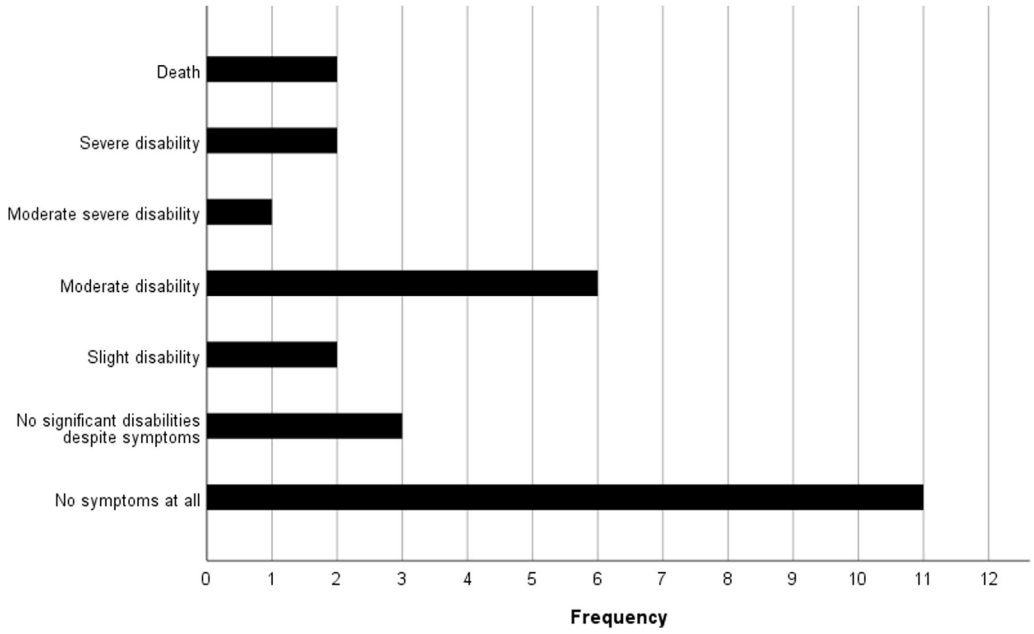

FIGURE 3. Modified Rankin Scale for children with stroke. The bar graph shows the frequency of modified Rankin scale scores for n = 29 Nigerian children with sickle cell disease.

(increase in MCV ≥10.0 fL) was not different by recurrence (56.3% in those without recurrence, 80.0% in those with recurrence, $P = 0.61$). Unlike in a clinical trial, no specific strategy was used to reinforce adherence to hydroxyurea, and hydroxyurea therapy was not provided to children as a trial therapy.

The mRS shows a wide degree of neurological disability after stroke in children with SCA

The mRS was assessed in 93% (27 of 29) of children with strokes, two of these children were deceased (mRS = 6). The median mRS was 1, range zero to six. Figure 3 shows the distribution. Classifying the mRS as either no or slight disability (zero to two), or moderate disability or worse (three to six), 75.0% (six of eight) of those with recurrence had moderate or greater disability compared with 26.3% (five of 19) of those without recurrence ($P = 0.033$). On the gross motor function classification system[9] 34.0% (10 of 25) had normal function and 21.0% (six of 25) had level three or higher. Both measurements were completed at a median of 1.6 years (IQR 1.9 years) after the initial stroke (Table). Despite the medical staff being trained on the PedNIHSS Scale before the beginning of the quality improvement project, no participants presenting with acute stroke symptoms were evaluated with the stroke scale. We did not identify this gap in assessment until completion of the quality improvement project.

Discussion

Despite the high prevalence of SCD in Nigeria and other sub-Saharan African countries, no standard strategy has been endorsed for secondary prevention of strokes. Using an accepted strategy for secondary stroke prevention in the absence of regular available blood transfusion therapy, in 2014, we introduced a uniform protocol for secondary stroke prevention in our tertiary care hospital and collected information describing our quality improvement program. The reported rate of initial strokes for our study was 0.88 events per 100 patient-years, which is similar to the expected incidence rate of 0.76 in children aged greater than 20 years[4] living in the United States in the era before primary stroke prevention for children with SCA with annual surveillance for abnormal TCD measurements, coupled with regular blood transfusion therapy. The recurrence rate of stroke when on hydroxyurea was 17.4 events per 100 patient-years, which falls less than the expected rate of 29.1 events per 100 patient-years in children without any treatment.[4,6]

TABLE.
Demographics of the Cohort Stratified by Occurrence of a Second Stroke (n = 29)

Variables	No Second Stroke (n = 21)	Second Stroke (n = 8)	*P* Value
Sex, male, n (%)	12 (57.1)	6 (75.0)	0.671*
Age at start of follow-up, median (IQR)	4.7 (6.6)	4.1 (2.4)	0.922†
Age at first stroke, median (IQR)	6.5 (7.3)	5.1 (3.3)	0.495†
Hydroxyurea use within 2 months of first stroke, n (%)	21 (100.0)	6 (75.0)	0.069*
Modified Rankin scale—moderate or severe disability, n (%) (n = 27)	5 (26.3)	6 (75.0)	0.033*
GMFCS (level 0—normal functioning), n (%) (n = 25)	9 (50.0)	1 (14.3)	0.179
Death, n (%)	1 (4.8)	1 (12.5)	0.483*

Abbreviations:
GMFCS = Gross motor function classification system
IQR = Interquartile range
* Fisher's exact test.
† Mann-Whitney test.

In our study, the majority (75%) of the stroke recurrences occurred within six months of the initial stroke. These findings are similar to prior evidence in children with SCD that highest incidence of stroke recurrence occurred within 24 months of the initial stroke for both individuals not receiving blood transfusion therapy,[4] and for those who do receive blood transfusion.[12]

At least two reasons, independently or together, may explain a higher rate of stroke recurrence after treatment with fixed moderate dose of hydroxyurea, 17.4 versus an expected rate of stroke recurrence of 3.8 events per 100 patients from a pooled analysis.[6] First, all expenses associated with hydroxyurea including the cost of the therapy and the cost of laboratory surveillance must be paid out of pocket by families. As shown in a recent study in Benin, Nigeria, another state without government-supported public health insurance, 16% (four of 24) of adults were compliant with hydroxyurea therapy. Major reasons for noncompliance were lack of funds and poor knowledge of adults with SCA regarding stroke prevention.[13] In our feasibility trial for primary stroke prevention in Nigerian children with SCA, which provided both free hydroxyurea and free laboratory evaluation, none of the scheduled monthly visits (603 visits) were missed and approximately 85% of the participants increased their MCV to greater than 10 fL from baseline suggesting good compliance with hydroxyurea.[5] The results of the present study demonstrate a poor adherence rate of only approximately 60% when the hydroxyurea therapy was self-pay. A second explanation for the lower than expected benefit for secondary stroke prevention is that the dose of 20 mg/kg/day may be too low to prevent stroke recurrence.

None of the children in this cohort had myelosuppression as a result of hydroxyurea using a fixed moderate dose of 20 mg/kg/day. This finding suggests that laboratory monitoring for myelosuppression is not required and may help to reduce the financial burden these families experience. The absence of toxicity associated with a fixed dose of hydroxyurea is similar to our earlier findings in the primary stroke feasibility trial in the same region, demonstrating no significant toxicity associated with fixed dose of 20 mg/kg/day of hydroxyurea therapy.[5] In a low-resource setting, the absence of myelosuppression is critically important because laboratory surveillance costs are typically paid for out of pocket. In this region, the mean monthly income is the equivalent of $130. A complete blood cell count is approximately $5.00, too expensive for many families to afford on a regular basis. Thus the maximum tolerated dose of hydroxyurea with monitoring for myelosuppression that is often used in high-income countries is perhaps too costly when combining the potential small incremental clinical benefit and the added burden of frequent laboratory monitoring. There is evidence that moderate dose of hydroxyurea (20 mg/kg/day) has clinical benefit in decreasing acute vaso-occlusive pain events and lowers TCD velocities.[5,14,15] The Pediatric Hydroxyurea Phase 3 Clinical Trial (BABY HUG) data also demonstrated that infants and young children on hydroxyurea therapy at a fixed dose of 20 mg/kg/day had no increased adverse events when compared with children not receiving any therapy.[15]

As part of the standard care assessment, we asked the pediatric staff specifically trained in the PedNIHSS scale to assess each suspected acute stroke in a child with SCA. However, no acute assessment with the scale was performed. The absence of any assessment with the stroke scale most likely reflects a lack of perceived clinical utility for the treating medical providers. Improvement in the acute care assessment of children with strokes represents an opportunity for the next cycle of quality improvement for stroke detection and management.

We were able to prospectively record the mRS on 93% (27 of 29) of children who had a stroke via parental interview and examination of the child to determine the degree of neurological disability after the stroke. Nine children (36%) had moderate to severe disability requiring assistance in walking and other daily activities including dressing, eating, and toileting. A total of 10 children (34%) had complete recovery from stroke. In a previous retrospective study in Ibadan, Nigeria, of 39 children who had stroke between 1998 and 2002, only 15% (six of 39) had complete recovery, with most children having mild to moderate disability requiring assistance with daily activities.[16] This degree of disability is similar to the findings by Njamnshi et al.[17] in Cameroon, who showed high stroke severity among patients with SCD because of lack of standardized care for managing SCD patients with stroke. None of these studies included cognitive assessment after a stroke, a major limitation in determining outcome after a stroke for children with SCD.

The stroke mortality rate of 4.3 per 100 patient-years for patients on hydroxyurea is similar to our previous findings in the primary stroke prevention in Nigeria trial in children with SCA. In this prior trial conducted in the same region, the mortality rate for children treated with hydroxyurea for primary stroke prevention was 2.69 per 100 patient-years and 1.81 per 100 patient-years in the comparison group of children without hydroxyurea therapy.[5] Similarly Makani et al.[18] found a mortality rate of 1.9 per 100 person-years in the general population of children with SCD in Tanzania. Mortality rates in high-income countries are at least 10 times lower, approximately, 0.15 per 100 person-years in the United Kingdom and 0.6 per 100 person-years in the United States.[19,20] Preliminary data suggest that death rate after a second stroke was much higher than expected, but these data are limited because of the low number of deaths after the second stroke ($n = 1$) and the short follow-up period (~1.3 years).

As expected in a quality improvement project, our study has inherent limitations. As data were collected primarily from clinical records, we included and analyzed only data captured and available in the clinical records. In addition, the clinical records were only paper-based with no electronic database. Consequently, we may have underestimated the number of strokes and deaths that occurred at home or at other hospitals outside our study site.

Given the high prevalence of strokes in unscreened and untreated children with SCA, primary and secondary stroke prevention programs are urgently needed for children with SCA living in Nigeria. Hydroxyurea may be a reasonable option for secondary stroke prevention; however, without a government policy to provide hydroxyurea therapy and laboratory surveillance for toxicity, this stroke prevention strategy is not likely to be effective in a low-resource setting. Furthermore, the optimal dose of hydroxyurea still needs to be elucidated for low-resource settings.

As the local expertise for detecting stroke has continued to grow at multiple institutions in the region, so has the number of children with SCD identified with stroke. After closure of the present study in July 2017 at AKTH, we created stroke care teams at the other two hospitals in Kano, Nigeria, Murtala Muhammad Specialist Hospital (start date August 2017) and Hasiya Bayero Pediatric Hospital, Kano, Nigeria (start date November of 2017). Subsequently, we identified an additional, seven, 29, and 20 strokes in children with SCD at the three hospitals, respectively. All children have been prescribed hydroxyurea at a fixed dose of 20 mg/kg/day. However, without a comprehensive public health strategy with a partnership including the state health department, the full benefit of primary and secondary prevention strategies will fall short of their potential in children with SCD.

Acknowledgments

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