Arteriopathy influences pediatric ischemic stroke presentation, but sickle cell disease influences stroke management

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ABSTRACT:
Background and Purpose: Sickle cell disease (SCD) and arteriopathy are pediatric stroke risk factors that are not mutually exclusive. The relative contributions of sickled red blood cells and arteriopathy to stroke risk are unknown, resulting in unclear guidelines for primary and secondary stroke prevention when both risk factors are present. We hypothesized that despite similarities in clinical presentation and radiographic appearance of arteriopathies, stroke evaluation and management differ in children with SCD compared to those without SCD.

Methods: We compared presentation and management of children with and without SCD enrolled in the International Pediatric Stroke Study with acute arterial ischemic stroke, according to SCD and arteriopathy status. Regression modeling determined relative contribution of SCD and arteriopathy in variables with significant frequency differences.

Results: Among 930 childhood arterial ischemic strokes, there were 98 children with SCD, 67 of whom had arteriopathy, and 466 without SCD, 392 of whom had arteriopathy. Arteriopathy, regardless of SCD status, increased likelihood of hemiparesis (OR 1.94; 95% confidence intervals [CI] 1.46, 2.56) and speech abnormalities (OR 1.67; CI 1.29, 2.19). Arteriopathy also increased likelihood of headache, but only among those without SCD (OR 1.89; CI 1.40, 2.55). Echocardiograms were less frequently obtained in children with SCD (OR 0.58; CI 0.37, 0.93), but the frequency of identified cardiac abnormalities were similar in both groups (p=0.57). Children with SCD were less likely to receive antithrombotic therapy, even in the presence of arteriopathy (OR 0.14; CI 0.08, 0.22). Arteriopathy was associated with a significantly higher likelihood of antithrombotic therapy in children without SCD (OR 5.36; CI 3.55, 8.09).

Conclusion: Arteriopathy, and not SCD status, was most influential of stroke presentation. However, SCD status influenced stroke management, as children with SCD were less likely to
have echocardiograms or receive antithrombotic therapy. Further work is needed to determine whether management differences are warranted.
Introduction

Stroke in children is often multifactorial, resulting from a culmination of systemic, anatomic, and possibly other provocations disrupting normal blood flow and oxygen delivery. Children with sickle cell disease (SCD) often have more than one risk factor for arterial ischemic stroke (AIS): systemic chronic disease that provokes ischemia throughout the body, as well as additional anatomic variations, such as arteriopathy or cardiac abnormalities. Arteriopathy increases both risk and stroke burden in children with SCD.

Current SCD guidelines recommend chronic transfusion therapy to suppress Hb S to less than 30% for primary and secondary stroke prevention, without clear distinction of the additional risk factor of arteriopathy. SCD guidelines neither recommend nor discourage antithrombotic use for primary or secondary stroke prevention with or without arteriopathy. However, the American Heart Association guidelines recommend consideration of aspirin or other antithrombotic therapy for secondary prevention of AIS in children, particularly those with arteriopathies, without distinction of other underlying systemic diseases contributing to arteriopathy development. Whether or not antithrombotic therapy provides additional benefit for children with SCD and arteriopathy, who have increased risk and burden for cerebral ischemia, remains controversial. Both American Heart Association and American College of Chest Physicians pediatric arterial ischemic stroke management guidelines recommend heparin or aspirin (for secondary stroke prevention in non-SCD patients) until a cause is determined and/or cardioembolic source and dissection are excluded.

Among all children with AIS, Goldenberg et al. found wide geographic variation in antithrombotic practice for secondary stroke prevention among pediatric stroke centers, with most prescribing at least one acute antithrombotic, but children with SCD and AIS were still less
likely to receive any antithrombotic therapy. Some providers may consider SCD as “cause determined” and therefore not needing antithrombotic therapy as recommended by the guidelines. However, whether SCD alone is sufficient explanation for a stroke is controversial, particularly with current screening and primary prevention practices significantly decreasing stroke incidence among children with SCD. A contributing factor to these controversies is an incomplete understanding of the relative contributions of systemic and anatomic factors to pediatric stroke presentation and management. To address this gap, we utilized the International Pediatric Stroke Study (IPSS) to compare AIS presentation in children with SCD with and without arteriopathy to children with AIS without SCD with and without arteriopathy. In order to understand current practices, we also compared diagnostic workup and secondary stroke prevention management. Based on previous findings of variation of antithrombotic management, we hypothesized that despite similarities in presentation, acute stroke management would differ between children with and without SCD.

Methods
The institutional review board at each site approved participation. Participants or guardians provided written consent. Data is available upon request from the authors.

Participants
IPSS, a prospective international registry, enrolled 4294 children and neonates from January 1, 2003 to July 31, 2014. We reviewed data on all children with acute AIS, excluding participants with neonatal or perinatal stroke. To minimize bias of resource availability, we included only children from sites that also enrolled SCD cases. We excluded children with
congenital or acquired cardiac disease listed as the primary etiology for AIS to decrease possible confounding of antithrombotic indication.

Local investigators collected and reported data, including SCD status and clinically obtained radiographic findings. Data included age at stroke, presenting symptoms, radiographic modality and findings, complete blood counts, medical co-morbidities, and acute medical treatment, defined as initiation of antithrombotic or thrombolytic treatment. The first imaging confirming the AIS diagnosis was recorded as the diagnostic scan. As neuroimaging is not available, we defined a participant as having an arteriopathy if an investigator reported the presence of stenosis, occlusion, focal cerebral arteriopathy, dissection and/or moyamoya disease. We assumed findings not reported were absent. We do not report long-term outcomes, including stroke recurrence, because follow-up data collection was variable.

We divided subjects into four groups based on SCD and arteriopathy status: 1) non-SCD, non- arteriopathy (-SCD-A), 2) SCD non-arteriopathy (+SCD-A), 3) non-SCD arteriopathy (-SCD +A), and 4) SCD arteriopathy (+SCD+A).

Statistics

Chi-square and Mann-Whitney U test compared categorical and continuous variables respectively, with significance considered at p<0.05. We applied a Bonferroni correction for multiple comparisons. To understand the relative contribution of SCD and arteriopathy to presentation and management decisions, variables that were significantly different, based on group-wise Chi-Square or Mann-Whitney U tests, were modeled in a generalized linear mixed random effects model with a binomial distribution and logit link (Glimmix procedure), with fixed effects of SCD status, arteriopathy status, and an interaction term between SCD and
arteriopathy status using SAS 9.4 (SAS Institute, Inc., Cary, NC). Results generated odds ratios, which we report with 95% confidence intervals.

**Results**

IPSS enrolled 98 children with SCD and AIS across 26 sites, which also enrolled 858 other non-cardiac AIS; arteriopathy was present in 459 including 67 with SCD and 392 without SCD. Group division based on risk factors resulted in 466 children -SCD-A, 31 +SCD-A, 392 -SCD+A, and 67 +SCD+A (Figure). Moyamoya and stenosis more frequently occurred in children with SCD, whereas dissection was more common in children without SCD (p <0.001).

**Presentation**

Hemiparesis, visual deficit, speech abnormality, and headache at stroke presentation differed among the four groups, but not ataxia or seizure at stroke onset (Table). In regression modeling of these features, arteriopathy, regardless of SCD status, increased likelihood of hemiparesis (OR 1.94 95% CI 1.46, 2.56, p <0.001) and speech abnormalities (OR 1.67; 95% CI 1.29, 2.19; p <0.001), but decreased likelihood of visual deficits (OR 0.60, 95% CI 0.45, 0.81; p=0.02). Neither SCD nor arteriopathy were independently significantly associated with headache, but an interaction found arteriopathy increased likelihood of headache in children without SCD (OR 1.89 CI 1.40, 2.55; p <0.001), but not among children with SCD (OR 0.66; CI 0.24, 1.79, p=0.41). As stenosis, occlusion, and moyamoya comprised 97% of arteriopathies in SCD, we performed a subanalysis limited to children with at least one of these arteriopathies (n=407). There was no difference between children with and without SCD for hemiparesis
(p=0.14), vision (p=0.40), speech (p=0.79), but children with SCD were less likely to report headache (OR 0.57 CI 0.35, 0.95, p =0.007).

**Diagnostic workup**

Echocardiogram was less commonly obtained during stroke admission in children with SCD (OR 0.58; 95% CI 0.37, 0.93; p = 0.02), but there was no difference of frequency of abnormalities, including patent foramen ovale (PFO), among groups. Conventional angiogram was more frequent among groups with arteriopathy, however odds ratios could not be calculated as no +SCD –A had an angiogram (Table).

**Treatment**

Although all enrolling centers treat acute stroke in SCD with transfusion as standard of care, further detailed information was unavailable. Antithrombotic initiation significantly varied among groups. SCD children, regardless of arteriopathy status, were less likely to be prescribed any antithrombotic therapy (OR 0.14; CI 0.08, 0.22; p<0.001) than those without SCD. Among children with arteriopathy, 92% of children –SCD+A received antithrombotic therapy, versus only 42% of +SCD+A children (p<0.001). Arteriopathy was associated with a higher likelihood of any antithrombotic treatment in children without SCD (OR 5.36; CI 3.55, 8.09; p<0.001), but not in children with SCD (OR 1.31; CI 0.54, 3.19; p=0.56). On further specification of antithrombotic therapy, arteriopathy conferred a higher likelihood of anticoagulation (any unfractionated heparin, low molecular weight heparin, or Coumadin), only in children without SCD [-SCD+A: (OR 4.36; CI 3.25, 5.86; p <0.001), +SCD+A (OR 0.75; CI 0.17, 3.37, p=0.71)]. Aspirin was the most common antithrombotic across all groups (Table), but children with SCD
were less likely to receive aspirin (OR: 0.37; CI 0.23, 0.62; p <0.001). Arteriopathy conferred a modest increase of likelihood to receive aspirin, but only when limited to children without SCD (OR: 1.14; CI:1.05, 1.81; p=0.02). Due to differences of types of arteriopathies reported between those with and without SCD, we analyzed to the 407 children with stenosis, occlusion, or moyamoya reported to determine whether or not type of arteriopathy was influencing treatment differences: Children with SCD were still less likely to receive either aspirin (OR 0.32 CI: 0.2, 0.56; p <0.001) or anticoagulation (OR 0.07; CI 0.03, 0.18, p<0.001).

**Discussion**

Systemic factors, in this case SCD, and anatomic factors, in this case arteriopathy, each have unique contributions to pediatric AIS. Despite similar presentation in children with arteriopathy with and without SCD, workup and management differed significantly, particularly in diagnostic workup and prescribing antithrombotic therapy.

Presentation differences among groups may reflect distinct processes leading to ischemic vulnerability. The lack of stroke presentation differences between –SCD+A and +SCD+A, with the exception of headache, highlights the importance of arteriopathy. Our finding of low headache frequencies in SCD subgroups is consistent with previous studies demonstrating lack of correlation between headache and ischemia in SCD. Adaptation to chronic pain in SCD is one potential explanation for the difference, but the pathophysiology contributing to headache and stroke in all children warrants further investigation.

Children with SCD were less likely to undergo echocardiogram than children without SCD, despite exclusion of children with cardiac-related AIS. As we restricted our study to centers with SCD enrollees to minimize differences in resource availability, we suspect fewer
echocardiograms in children with SCD reflects a belief that SCD is sufficient to explain stroke and no further risk factor workup is necessary. However, among those who had an echocardiogram, there was no difference in detection of abnormalities, with almost 20% of the entire cohort having an abnormality noted. This counters the assumption that children with SCD would be unlikely to have echocardiogram findings. PFO was the most common abnormality, consistent with previous work. While the contribution of PFO to pediatric stroke is not established, a recent study of adult cryptogenic stroke age 16 to 60 years and PFOs associated with atrial septal aneurysm or large interatrial shunt demonstrated PFO closure reduced stroke recurrence. Given the low number of echocardiograms performed in all groups, there appears to be an under-appreciation of this potential risk factor, particularly within the SCD population.

A prior analysis of the initial 640 childhood AIS subjects enrolled in the IPSS between 2003-2007 (some of whom are included in the current analysis, including 19 children with SCD), found that moyamoya increased and SCD decreased the likelihood of antithrombotic use, despite overlap in these conditions. Our study again demonstrates infrequent antithrombotic therapy in SCD, even in the presence of arteriopathy. Dissection and focal cerebral arteriopathy, for which antithrombotic therapy is recommended, were not diagnosed in SCD, perhaps because they were included in the stenosis category or investigations such as fat-saturation T1-MRI of the neck or conventional arteriography to exclude dissection in the neck were not ordered. It is important to note that our non-SCD groups represent only a subset of children with and without arteriopathy within the current IPSS database. We used this subset to eliminate confounding of center-specific practice variation in SCD stroke treatment comparison, and as a subset, the practices reported here may or may not be consistent with the larger cohort of non-SCD children, which is outside the scope of this analysis.
Reasons for the discrepancy in antithrombotic management are unknown, but may include lack of specific evidence and guidelines, or concern that antithrombotic therapies carry more risk than benefit. Guidelines for SCD and for arteriopathy are separate and do not address the overlap of the two entities. Our finding that arteriopathy, but not SCD status, predicted features of stroke presentation suggests that arteriopathy should be considered a contributory risk factor to stroke in children with SCD. This finding warrants further investigation of stroke prevention strategies to mitigate this specific risk in children with SCD, such as aspirin or revascularization surgery. Transfusion therapy is standard of care for decreasing stroke risk after a child with SCD experiences a stroke (secondary prevention), regardless of arteriopathy status. However, transfusions may be insufficient for preventing recurrent stroke in the presence of a progressive arteriopathy. The current challenge is that guidelines exist for stroke management in SCD without qualification for arteriopathy status, and guidelines exist for arteriopathy management without qualification for SCD status. The two guidelines are not mutually exclusive, and many physicians, including authors, recommend both transfusion therapy and aspirin therapy to patients with SCD who have stroke and arteriopathy. Furthermore, while the role of antithrombotic agents has not been evaluated specifically in children with SCD, evidence of increased platelet activation in SCD suggests aspirin may be particularly beneficial in this population. One single-center study by Majumdar et al. specifically examined aspirin use in SCD overt strokes, and did not find a difference in stroke recurrence between those taking aspirin or not, but was limited by small numbers. Interestingly, a majority of patients were taking aspirin, and their overall stroke recurrence rate was much lower than previously reported stroke recurrence rates in SCD. Whether or not the higher risk of hemorrhagic stroke and aneurysm rupture in adulthood would alter the risk-benefit ratio of reducing AIS in childhood is
unknown, but the low hemorrhage rate in up to 18 years of follow up from Majumdar et al. suggests this may not be as significant as feared. An assessment of stroke hospitalization rates in adults with SCD from 2000-2014 found ischemic stroke hospitalization rates to be three times as high as hemorrhagic stroke, suggesting that in modern day treatment of SCD, adults and children with SCD may benefit from further efforts of ischemic stroke prevention.14

Our study has several limitations. The observational data is limited to what treating physicians deemed relevant, although this allows for reflection of actual practice. Not all children deemed arteriopathy absent had dedicated vascular imaging to confirm the lack of arteriopathy. However, decisions to not obtain dedicated vascular imaging likely reflects an assumption of lack of arteriopathy and would not change our findings about other management decisions. The database variables reflected the intent to understand pediatric stroke broadly, and did not capture data of interest to SCD-related stroke. For example, many SCD patients were likely transfused for stroke prevention, the database did not include relevant details of the specific type of SCD or transfusion status. This information would help understand the SCD cohort, but it would not change our conclusion that SCD stroke presentation is similar to pediatric stroke presentation without SCD, but differs in the investigative workup. Another limitation is the broad categorization of arteriopathy. In the CASCADE criteria, arteriopathies are subdivided into four distinct arteriopathy categories: small vessel arteriopathy of childhood, unilateral focal cerebral arteriopathy, bilateral cerebral arteriopathy, and aortic/cervical arteriopathy.15 However, IPSS data collection was initiated prior to CASCADE and radiographic images were not available for central review. Despite the broad categorization and recognized differences of types of arteriopathies between –SCD+A and +SCD+A, the similarities of presentation between these two groups remains high. MRA was the sole modality to diagnose
arteriopathy in many patients. Overestimation of arteriopathy may occur if narrowing was caused by turbulent flow rather than true arteriopathy, particularly in time-of-flight MRAs. While arteriopathy overestimation would explain our slightly higher prevalence of arteriopathy in 48% of our total stroke cohort, compared to other published populations,\textsuperscript{5,16} misclassification should diminish group differences. Therefore, we would not expect our conclusion of differences in stroke presentation and workup and management to change.

**Conclusion**

Arteriopathy is an important contribution to stroke presentation in children with and without SCD. Differences in management, particularly antithrombotic therapy, reflect a lack of unification of multiple risk factors within current guidelines and, possibly perceived separation of systemic and anatomic risk factors in children. Our data suggests that these differences may not be as great as perceived, and antithrombotic therapy may prove beneficial in a select subset of SCD patients. Further studies are needed to determine whether differences in evaluation and management based on SCD status are warranted, particularly among children with SCD and arteriopathy.

**Acknowledgements**

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References


Figure: Participant selection from International Pediatric Stroke Study database.
Table. Presentation and management according to sickle cell disease (SCD) status and arteriopathy. Raw p-values represent significance of differences among all four groups. Variables with bolded p-values are significant after correction for multiple comparisons. Odds ratios for contribution of SCD, arteriopathy, or the interaction of terms, as reported in text. CT= computed tomography MRI = Magnetic resonance imaging LMWH = low molecular weight heparin

<table>
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<th>p</th>
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<td>SCD (n=31)</td>
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<td>Age (years)</td>
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<td>8.2 (+/- 5.1)</td>
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<td>Moyamoya</td>
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<td>n/a</td>
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<td>44 (66%)</td>
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<td>Seizure</td>
<td>123 (26%)</td>
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<td>Conventional Angiogram</td>
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<td>MRA</td>
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<td>16 (50%)</td>
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<td>Anterior</td>
<td>271 (58%)</td>
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<td>174 (37%)</td>
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<td>134 (34%)</td>
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<td>2 (6%)</td>
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*Percentages may not equal 100%, as children may fall in more than one category.