Increased Prevalence of Potential Right-to-Left Shunting in Children with Sickle Cell Anemia and Stroke

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Abstract

"Paradoxical" embolization via intracardiac or intrapulmonary right-to-left shunts (RLS) is an established cause of stroke. Hypercoagulable states and increased right heart pressure, which both occur in SCA, predispose to paradoxical embolization. We hypothesized that children with SCA and overt stroke have an increased prevalence of potential RLS. We performed contrasted transthoracic echocardiograms on 147 children (ages 2-19y) with SCA and overt stroke (SCA+stroke; mean age 12.7±4.8 years, 54.4% male) and a control group without SCA or stroke (n=123; mean age 12.1±4.9 years, 53.3% male). RLS was defined as any potential RLS detected by any method, including intrapulmonary shunting. Echocardiograms were masked and adjudicated centrally. The prevalence of potential RLS was significantly higher in the SCA+stroke group than controls (45.6% vs. 23.6%, $p<0.001$). The odds ratio for potential RLS in the SCA+stroke group was 2.7 (95% confidence interval: 1.6-4.6) vs controls. In *post hoc* analyses, the SCA+stroke group had a higher prevalence of intrapulmonary (23.8% vs. 5.7%, $p<0.001$) but not intracardiac shunting (21.8% vs. 18.7%, $p=0.533$). SCA patients with potential RLS were more likely to report headache at stroke onset than those without. Intrapulmonary and intracardiac shunting may be an overlooked, independent, and potentially modifiable risk factor for stroke in SCA.

Introduction

Children with sickle cell anemia (SCA) are at high risk of ischemic stroke, the causes of which are still not fully understood (Roach, et al., 2009). This high risk must be driven, at least in part, by the adverse effects of sickle hemoglobin. Until recently, any additional role for the "traditional" risk factors for stroke (identified in the general population) has not been considered clinically or studied in children with SCA and stroke (Dowling, et al., 2009). In children and young adults

without SCA, “paradoxical” embolization is an established cause of stroke. By this mechanism, emboli from the venous circulation escape filtration by the lungs and pass from the right heart directly to the left heart and on to the brain (Overell, et al., 2000; Benedik, et al., 2007; Dowling and Ikemba, 2011; Ning, et al., 2013). Such right-to-left shunting (RLS) can occur via a patent foramen ovale (PFO), any other intracardiac shunt, or intrapulmonary shunts, such as pulmonary arteriovenous malformations. The risk of paradoxical embolization is increased by hypercoagulable states and elevated right heart pressures, both of which may occur more often in children with SCA (Ning, et al., 2013; Hassell, 2005; Ataga and Orringer, 2003).

In a pilot study, we found a higher prevalence of potential right-to-left shunting in children with SCA and stroke than in a comparison group of children without SCA who also had stroke (Dowling, et al., 2010). There are few control data available on the prevalence of potential shunting in children without stroke (Dowling and Ikemba, 2011). We sought to determine if paradoxical embolization could be a risk factor for stroke in children with SCA by evaluating a large population of children with SCA and stroke and a control group of children without SCA or stroke by standardized contrast echocardiographic methods in a prospective multicenter study. We hypothesized that the prevalence of potential right-to-left shunting detected by contrast transthoracic echocardiography would be higher in children with SCA and stroke than in a control population of children without SCA or stroke.

Methods

We performed a cross sectional study of children with a diagnosis of SCA [defined here as homozygous sickle cell anemia (HbSS) or sickle-β^0-thalassemia] and a history of clinically overt ischemic stroke (acute or remote) as well as controls without SCA or history of stroke to evaluate for potential right-to-left shunting by contrasted transthoracic echocardiogram (TTE). Local Ethics or Institutional Review Board approval was obtained at all 14 institutions in the US

and UK (see Acknowledgements). We enrolled children 2-19 years of age who had intravenous (IV) access obtained for another clinical indication (e.g. blood transfusion, hydration, or administration of IV medication). Informed consent, and assent when appropriate, was provided by all participants or their parents.

We chose a control group of children without SCD and without history of stroke for reasons of feasibility, along with financial and ethical limitations. Our Institutional Review Board would not permit placement of an intravenous line required for the administration of agitated saline contrast for the echocardiogram solely for the purposes of this study, where there was presumed to be no clinical benefit. Thus, while children with SCD frequently receive venipuncture, we were not allowed to leave an IV in place for the study at the time of simple venipuncture. There had to be another clinical indication for the IV to remain in place and the children had to be "healthy" at the time of the study. This precluded the study of shunting in children with SCA without overt stroke who were not acutely ill. Thus, there were limited opportunities to enroll children with SCA without stroke in the study and we chose a control group of children without SCD or stroke who had an IV in place for another clinical indication. Within these parameters, we were able to enroll children with SCD and stroke on chronic transfusion programmes where the echocardiogram could be scheduled in advance in conjunction with planned transfusions for which an IV would be in place. For control subjects, the same requirements were in place. Many of our control patients were drawn from populations scheduled for planned procedures, minor surgeries, imaging studies, or infusions that required planned placement of an IV.

Further, clinically silent stroke is highly prevalent in children with SCA (DeBaun, et al., 2014) and this could be related to RLS as well. We felt that children with SCA would require screening for silent infarction for inclusion as control subjects. Our study budget did not allow for MRI to

evaluate for the presence of silent cerebral infarction in the control group but this was assumed to be a low frequency event in our control group of children without SCA.

We defined stroke as a focal neurologic deficit of acute onset with a corresponding abnormality on CT or MRI in a location consistent with the neurologic signs and symptoms. Children with SCA and only silent cerebral infarctions (those identified only by imaging study without any corresponding focal neurologic abnormalities) were not included. For control subjects we excluded those with known or suspected congenital heart disease and those undergoing echocardiogram for transient ischemic attack, migraine headache, or other neurologic indication. Additionally we excluded patients who were clinically unstable for echocardiogram or had undergone surgical closure of any intracardiac shunts.

Transthoracic echocardiograms were performed by standardized methods at the local sites and included conventional 2-D, color Doppler, and a total of 4 IV contrast injections with agitated saline, including 2 at rest and 2 with Valsalva maneuver. For the contrast injections, peripheral IV or indwelling “ports” were used to administer agitated saline (5ml for patients <45 kg, 10 ml for patients >45 kg). Images were recorded in a 4-chamber view by standard technique (Woods and Patel, 2006). A minimum of 5 seconds recording was obtained to allow the contrast to reach the heart and ≥5 cardiac cycles were reviewed. Potential right-to-left shunts were defined as the detection of any shunting, in any direction, by any method, including 2-D, color Doppler, or any one of the 4 contrast injections. Intrapulmonary shunting, characterized by the detection of “late bubbles” (detection of contrast in the left atrium or ventricle 5 cardiac cycles after the appearance of contrast in the right heart) is also included as potential RLS. Patient age, weight, height, heart rate, blood pressure and oxygen saturation by pulse oximetry were recorded at the time of the echocardiogram.

Echocardiograms were analyzed at the local site then de-identified for masked central review by the study cardiologist. In the event of conflicts between local and central interpretations, the studies were re-reviewed with a third masked evaluator and consensus was obtained. All echocardiograms where potential shunting was identified were re-reviewed to confirm and classify the potential shunting as intracardiac or intrapulmonary.

Demographic as well as clinical history and laboratory data were collected by medical record review and patient/parent interview using standard case report forms. Data were checked by dual entry techniques, with identification of outliers and query of the local sites.

Based on published data and the results of our pilot study (Dowling and Ikemba, 2011; Dowling, et al., 2010) a minimum of 160 patients per arm (320 total) were needed to detect a prevalence of RLS estimated at 19.99% for SCA+stroke patients and 9% for controls assuming a Type I error of .05 and 80% power using a 2 sided, independent samples Z test for proportions; alternatively this same sample size estimate for chi-square resulted in 81.8% power. We closed study enrollment when all eligible patients at the study sites had been enrolled or screened. Final study enrollment after exclusion of cases was 270 (see below).

The prevalence of potential RLS in the two groups was compared using Chi-square or Fisher's exact test, as appropriate. The clinical and demographic data obtained by review of the medical record and patient/parent questionnaires were analyzed for association with shunting using Chi-square or Fisher's exact test for categorical, and Student's t-test or Mann-Whitney U test for continuous variables, as appropriate. Subjects and controls were not matched by age, gender, or race. Prior studies report that age is an important factor in the prevalence of patent foramen ovale but sex and race are not (Dowling and Ikemba, 2011). We re-evaluated this with additional analyses that explored the influence of demographic features (group, sex, race, and age at echo) on the prevalence of potential shunting or pulmonary shunting using logistic

regression models. The assumptions for all statistical analyses were examined for violations. A p-value of <0.05 was considered significant for the primary and secondary analyses which were performed using IBM SPSS version 23.0.

Results

Characteristics of Participants

We enrolled and evaluated 283 children. Thirteen participants were excluded from the analysis (8 with SCA+stroke and 5 controls) for inadequate echocardiogram or inadequate contrast studies. Data from 147 children with SCA+stroke and 123 controls were analyzed. There were no adverse events reported during the study echocardiograms.

There were no significant differences in age or gender between the two groups, except the expected difference in racial distribution (Table 1). Most children with SCA+stroke were enrolled several years after their initial stroke; mean age at stroke was 6.2 years with echocardiogram performed at a mean age of 12.7 years.

Frequency of Potential Right-to-Left Shunting

There was a significantly higher prevalence of potential shunting in the SCA+stroke group (45.6% vs. 23.6% in controls p<0.001, Table 2). Contrast injection increased the detection rate for potential shunting in both groups, but the addition of Valsalva maneuver had minimal effect. There was a higher prevalence of intrapulmonary shunting (“late bubbles” only) in the SCA+stroke group (23.8% vs. 5.7% in controls, p<0.001) but not intracardiac shunting (21.8% vs. 18.7%, p=0.533).

Risk Factors for Potential Right-to-Left Shunting

Logistic regression analyses demonstrated that age at echocardiogram and sex were not significant predictors of any potential shunting when both groups were included in the analysis ($p>0.6$) or of intrapulmonary shunting when the SCA/stroke group was included in the analysis ($p>0.5$). Race (Black vs. White) was not a predictor of potential shunting when the control group was included in the analysis ($p>0.4$). In the final model predicting any potential shunting, only group (SCA+stroke vs. controls) was predictive for the presence of any potential shunting. Those with any potential shunting were 2.7 times more likely to be in the SCA/stroke group compared to Controls than those without any potential shunting [odds ratio (OR) = 2.7; 95% confidence interval (CI), 1.6-4.6].

Clinical Correlates of Stroke in Participants with Potential RLS

We also compared the demographic, clinical, and laboratory data of the SCA+stroke group with and without potential RLS (Table 3). Headache was reported at the time of onset of stroke in 48% of those with shunting vs. 27% of those without ($p=0.021$). There were no other significant differences between those SCA+stroke patients with and without RLS. There was no difference in patient-reported ongoing “bad headaches or migraine” at the time of the echocardiogram ($p=0.888$). There also was no difference in the prevalence of recurrent stroke or TIA between those with and without shunting.

We studied these same demographic, clinical, and laboratory data in the SCA+stroke group with and without intrapulmonary shunting only. There was a higher prevalence of a patient/parent reported diagnosis of obstructive sleep apnea in those with intrapulmonary shunting (6/34 (17.6%) vs. 6/109 (5.5%)) than in those without ($p=0.036$). There were no differences, however, in patient/parent-reported snoring, asthma, diagnosis of pulmonary hypertension, or hemoglobin oxygen saturation.

Discussion

We identified a high prevalence of potential right-to-left shunting in children with SCA and stroke compared to a control group of children without SCA or stroke. Potential right-to-left shunting was 2.7 times more likely in the children with SCA and stroke (95%CI 1.6-4.6). The difference in prevalence of potential RLS between cases and controls appeared to be driven by higher prevalence of extra-cardiac, intrapulmonary shunts in cases with SCA and stroke. Among children with SCA and stroke, those who had any potential RLS were almost twice as likely to recall having a headache at the onset of their stroke as children with SCA and stroke without potential RLS. Intrapulmonary and intracardiac shunting could be an overlooked, independent, and potentially modifiable risk factor for stroke in children with SCA.

Paradoxical embolization via patent foramen ovale is an established risk factor for stroke in young adults and children without SCA (Dowling and Ikemba, 2011; Ning, et al., 2013; Mattle, et al., 2010). Meta-analysis of 15 studies showed that adult stroke patients were 1.69 times (CI 1.40-2.06) more likely to have a PFO than non-stroke controls (Mattle, et al., 2010). There are only limited studies of the prevalence of potential shunting in children with or without stroke (reviewed in Dowling and Ikemba, 2011). In our pilot study (Dowling, et al., 2010) retrospective chart review found potential shunting in 11.7% (7/60) of children with stroke who did not have SCD (excluding children with known congenital heart disease). Benedik and colleagues (2011) reported on transesophageal echocardiograms with contrast as well as using contrasted transcranial Doppler ultrasonography and reported potential shunting in 7/26 (27%) of controls compared with 11/23 (48%) of children with stroke or TIA (without SCD) excluding those with other identified aetiologies for stroke. Intrapulmonary shunting alone was an independent predictor of cryptogenic stroke or TIA in adults without SCA compared to controls (OR 2.6 (CI 1.6-4.2)) (Abushora, et al., 2013). Prothrombotic states predispose to paradoxical embolization in adult patients with potential intracardiac shunting (Hassell, 2005; Giardini, et al., 2004; Karttunen, et al., 2003) and the Valsalva maneuver, which can increase right heart pressures

and favor right-to-left shunting, is common at the onset of stroke in adults without SCA (Karttunen, et al., 2003; Bogousslavsky, et al., 1996).

There are several physiologic features of SCA that may serve to predispose to stroke by paradoxical embolization. First, SCA is, in itself, characterized by activation of coagulation. Old and new thrombi are observed in the pulmonary vasculature in postmortem studies of patients with SCA, illustrating the effective pulmonary filter. SCA patients have been shown to have high levels of circulating thrombin, activation of fibrinolysis, decreased levels of anticoagulant proteins, and platelet activation (Ataga and Orringer, 2003; Shah, et al., 2012; Ataga, et al., 2012; Colombatti, et al., 2013; Whelihan et al., 2014; Hyacinth, et al., 2015). Further, right-to-left shunting is favored in SCA given the pathophysiologic changes secondary to anemia and pulmonary venous or arterial hypertension, especially in the setting of acute chest syndrome. These conditions will raise right heart pressures, increasing the likelihood of right-to-left shunting and therefore potential for paradoxical embolization.

Prior studies of fat embolization syndrome in SCA also support the role of paradoxical embolization in stroke in SCA. Multiple scattered punctate MRI abnormalities, consistent with embolic phenomenon were reported in an SCA patient with fat embolization syndrome following vaso-occlusive crisis (Horton, et al., 1995). Neurologic symptoms, including focal signs and focal lesions on MRI, were noted in half of the patients with fat emboli detected by bronchoscopy in patients with vaso-occlusive crisis and acute chest syndrome, while none of the patients without pulmonary fat emboli had neurologic symptoms (Vichinsky, et al., 1994). The heart was not examined in these studies, but the only route for fat emboli to the brain is via cardiac or pulmonary right-to-left shunting. Indeed, fat emboli have been directly observed passing through a PFO during intraoperative echocardiogram in a patient without SCA undergoing surgical repair of a femoral fracture (Pell, et al., 1993).

The high prevalence of potential right-to-left shunting we identified in children with SCA and stroke, (45.6%) compared to that in our control group of children without SCA or stroke (23.6%) suggests that paradoxical embolization across an intracardiac or intrapulmonary shunt could be a risk factor for stroke in children with SCA. However, this increased prevalence of potential RLS could be due to changes common to all children with SCA and not causally related to stroke in this group. Further, the role of RLS in silent cerebral infarction is not known. We did not include children with silent cerebral infarction in this study. It is possible that there could be an even greater contribution from shunting to silent cerebral infarction than overt stroke. PFO has also been associated with silent cerebral infarction in adults without SCA (Clergeau, et al., 2009; Ueno, et al., 2010).

In a recent study of 29 SCA patients with first ischemic stroke in adulthood, 7/29 (24%) had cardiac embolism as an identified etiology for their stroke (Calvet, et al., 2015). Large PFO was identified in 3 patients, dilated cardiomyopathy in 1 and fat embolism in another patient. Stroke was attributed to vasculopathy in 12/29, antiphospholipid antibody syndrome in 1, and was undetermined in 8. Only 22/29 of these adults with SCA and stroke had echocardiograms. It was not reported if these were contrast studies. Our data (Table 2) clearly demonstrate that the addition of IV contrast dramatically increases the detection rate for potential shunting. As noted in studies of stroke in children without SCA, it is likely that individual patients have multiple stroke risk factors (Mackay, et al., 2011). More thorough etiologic investigations may reveal their presence in children and adults with SCA and stroke and offer opportunities for prevention. evaluate for OSA or nighttime hypoxaemia and most centres in this study did not, at the time of the study, evaluate their patients for OSA or nighttime hypoxaemia

We did not observe an association of potential shunting with recurrent stroke or TIA in our study. However, one fifth of our SCA patients had their echocardiogram within 2 years of index stroke, with several enrolled at the time of initial stroke presentation. This limited our ability to

detect a relationship between RLS and recurrent stroke. In the previously mentioned study of adults with SCA and stroke, 9/29 had recurrent stroke which was attributed to cardiac embolism in 4 cases. (Calvet, et al., 2015). In children with SCA, recurrent stroke is often attributed to moyamoya syndrome or progressive cerebral vasculopathy. However, stroke recurrence, as well as first time stroke, still occurs in the absence of vasculopathy, albeit at a lower rate (Hulbert, et al., 2011). In this subset of patients, paradoxical embolization may play a larger role, as appears to be the case in non-SCA childhood stroke, (Benedik, et al., 2007) and it must be noted that the presence of vasculopathy does not rule out paradoxical embolization as an etiology for stroke. Unfortunately, due to budgetary constraints, we did not obtain vascular imaging as part of this study.

Another important finding of this study is the high prevalence of intrapulmonary shunting in the SCA+stroke group. Intrapulmonary shunting was only discernable by our method in participants without concomitant intracardiac shunting, which may have obscured some relevant clinical associations. A similar high prevalence of intrapulmonary RLS was reported in adults with SCA (16% vs. 3.8% in general medical patients without SCA) (Langer, et al., 2013). Thus, this high prevalence of intrapulmonary shunting we observed may be common in children with SCA without stroke. Our control group was limited to children without SCA or stroke. Future studies of RLS in children with SCD without stroke are needed. In an exploratory analysis, we found that prior diagnosis of obstructive sleep apnea (OSA) was associated with intrapulmonary shunting, but our patients were not systematically evaluated for OSA. Intrapulmonary shunting was not associated with other indicators of lung disease or OSA such as patient reported snoring, asthma, diagnosis of pulmonary hypertension or low daytime hemoglobin oxygen saturation. We were not funded for polysomnography or overnight oximetry and most centres in this study did not, at the time of the study, evaluate their patients for OSA or nighttime

hypoxaemia but exploration of the possible association between OSA and/or nighttime hypoxaemia and RLS would be of interest in future studies.

Our study has several limitations. Research ethics considerations in children precluded placement of an IV solely for research, limiting our ability to evaluate children with SCA without stroke who were not acutely ill and is why we assembled a control group of children without SCA or stroke who already had IV access obtained for another clinical indication. The high prevalence of potential shunting we found could apply to all children with SCA, not just those with stroke. It also could be a marker of more severe disease and warrants further investigation. Future studies to compare the prevalence of potential RLS in children with SCA both with and without stroke or silent cerebral infarction are needed. Our study does provide much needed control data (Dowling and Ikemba, 2011) on the prevalence of potential shunting by contrasted echocardiography in a large population of children without stroke or other neurologic indications for testing. RLS is clearly not likely to be the only, or the major cause of stroke in children with SCA, but could be an important contributing etiology in some patients. Analysis of the contribution of concurrent illnesses, cerebral vasculopathy, and other potential stroke risk factors in this population is needed.

There was a substantial time period between onset of stroke and our evaluation by echocardiogram in many patients (Table 1). Autopsy studies show a decline in PFO prevalence with each decade, (Hagen, et al., 1984) so we may have underestimated the prevalence of intracardiac shunting at the time of stroke. However, our analysis found that age was not a predictor of “any shunting” or “intrapulmonary shunting” in our study population. We also did not statistically correct for multiple comparisons in our analysis of clinical and laboratory factors associated with shunting. The one factor we found to be significantly associated with shunting, namely headache at the time stroke onset, was also found in our pilot study, (Dowling, et al.,

2010) and intracardiac shunting has been associated with migraine in adults (Schwedt, et al., 2008).

There are clearly multiple independent risk factors for stroke in SCA, including vasculopathy, anemia (acute and chronic), and antecedent medical events, among others (Scothorn, et al., 2002; Kirkham, 2007; Quinn and Sargent, 2008; Dowling et al., 2012). In our study we did not stratify patients by these etiologies and MRI/A data was not included in our primary analysis. It is possible that shunting may have a pathologic role in specific stroke subtypes. Our observations, and recent studies in adults with SCA showing a high prevalence of cardioembolic etiologies for stroke (Calvet, et al., 2015) support paradoxical embolization via RLS as a possible cause of stroke in children with SCA.

In summary, potential right-to-left shunting is common in children with SCA and stroke. We recommend that all children with SCA and stroke be evaluated by contrasted echocardiography, especially those who have headache at onset. We propose that intracardiac and intrapulmonary right-to-left shunting is an overlooked, independent, and potentially modifiable risk factor for stroke in children with SCA. In addition to chronic transfusion or hydroxyurea therapy, additional methods to prevent stroke, such as anti-platelet therapy, anticoagulation, or shunt closure, need to be studied in children with SCA.

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Authorship Contributions

MMD designed the study, obtained funding, conducted the analysis and wrote the first draft of the manuscript.

CTQ participated in study design, wrote the first draft of the manuscript and participated as study committee member, and enrolled patients.

PP was overall study coordinator.

CR was the main study cardiologist who participated in study design and reviewed all study echocardiograms and participated in data analysis.

FK served as study consultant and participated in study design, obtained Ethics approval for the UK and participated in study design and analysis.

LSH was the study biostatistician and performed the study analysis.

The above and other authors participated in study design at investigator meetings, enrolled patients, contributed to the analysis of the data, and critically reviewed the manuscript.

Disclosure of Conflicts of Interest

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Table 1 Subjects

	SCA+Stroke	Control	P value
Age at Stroke Onset (mean yr ± SD)	6.2 ± 3.8	-	-
Age at Echocardiogram (mean yr ± SD)	12.7 ± 4.8	12.1 ± 4.9	0.326*
Gender (% male)	54.4	53.3	0.851*
Race Black (%) **Caucasian** **Asian** **Other**	99.3 0 0 0.7	25.7 64.6 4.4 5.3	<0.001†

*Student's independent samples t-test. †Fisher's Exact test based on comparison of Black vs all others.

Table 2 Prevalence of Potential Right-to-Left Shunt Detected in SCA+Stroke and Control Subjects

Method of Shunt Detection	SCA+Stroke # (%)	Control # (%)	P value*
2-D Imaging	3/139 (2.2%)	0/122 (0%)	0.250†
Color Doppler	9/139 (6.5%)	8/122 (6.6%)	0.978
Contrast Injection without Valsalva	22/146 (15.1%)	19/122 (15.6%)	0.909
Contrast Injection with Valsalva	24/145 (16.6%)	19/118 (16.1%)	0.922
Potential Intracardiac Shunting	32/147 (21.8%)	23/123 (18.7%)	0.533
Potential Intrapulmonary Shunting "Late Bubbles" only	35/147 (23.8%)	7/123 (5.7%)	<0.001
Any Potential Shunting (Intracardiac or Intrapulmonary)	67/147 (45.6%)	29/123 (23.6%)	<0.001

*Chi-square test, with Fisher's exact where indicated†

Table 3 Clinical Factors Present in SCA+Stroke Patients with and without Potential Shunt

Factor	Any Shunt Absent # (%)	Any Shunt Present # (%)	P value*
Age at Stroke Onset (years, mean±SD)	5.9 ± 3.5	6.6 ± 4.2	0.286•
Age at Echocardiogram (years, mean±SD)	12.4 ± 4.7	13.1 ± 4.9	0.336•
Gender (% male)	42/80 (52.5%)	38/67 (56.7%)	0.609*
Acute Illness at Onset or 2w prior to stroke	42/77 (54.5%)	33/63 (52.4%)	0.798*
TIA prior to onset	1/80 (1.3%)	2/67 (3.0%)	0.592†
Headache at stroke presentation	17/63 (27.0%)	24/50 (48.0%)	**0.021***
Ongoing Headache or Migraine	28/79 (35.4%)	23/67 (34.3%)	0.888*
Seizures (at presentation or subsequently)	19/80 (23.8%)	17/67 (25.4%)	0.820*
Stroke Outcome, PSOM (median, range)	0.5 (0-8)	0.5 (0-8)	0.943‡
Recurrent Stroke or TIA	27/80 (33.8%)	21/67 (31.3%)	0.757*
Hgb Oxygen Saturation (median, range)	99 (96-100)	99 (93-100)	0.310‡
Hx of Acute Chest Syndrome	34/73 (46.6%)	28/59 (47.5%)	0.920*
Hx of frequent pain crises (> 5)	22/69 (31.9%)	17/59 (28.8%)	0.707*
Hx of Gallstones	14/72 (19.4%)	10/54 (18.5%)	0.896*
Hx of Priapism (for males)	3/38 (7.9%)	7/34 (20.6%)	0.175†
Hx of Splenic Sequestration	13/72 (18.1%)	17/58 (29.3%)	0.130*
Hx of Aplastic Crisis	6/70 (8.6%)	7/53 (13.2%)	0.408*
Hx of Aseptic Necrosis	1/72 (1.4%)	3/59 (5.1%)	0.326†
Dx of Pulmonary Hypertension	2/69 (2.9%)	2/60 (3.3%)	>0.999†
Hgb Conc at/prior to stroke (median, range)	7.95 (5.0-13.9)	8.05 (2.4-13.7)	0.972‡
WBC at/prior to stroke ($x10^3$, median, range)	15.52 (4.4-42.4)	14.21 (4.7-41.3)	0.359‡
Plt at/prior to stroke ($x10^3$, median, range)	351.5 (114-763)	395.0 (92-1091)	0.833‡
HgbS% at/prior to stroke (median, range)	57.8 (5-100)	60.5 (6.3-100)	0.607‡
Retics % at/prior to stroke (median, range)	13.6 (3-31.8)	11.1 (1-20.1)	0.702‡
Any Family Hx of Hypercoagulable State	34/78 (43.6%)	35/65 (53.8%)	0.222*
Report of Snoring or Diagnosis of OSA	21/78 (26.9%)	22/67 (32.8%)	0.437*
Asthma	25/79 (31.6%)	20/66 (30.3%)	0.862*

•Student's independent samples t-test, ‡Mann-Whitney U test, *Chi-square test, or †Fisher's exact where indicated. Abbreviations: TIA= transient ischemic attack, WBC=white blood cell, Plt=Platelet, Retics = Reticulocytes, OSA= obstructive sleep apnea, Hx=History, Hgb= hemoglobin. PSOM= Pedi Stroke Outcome Measure (0= no deficit, 10= severe deficit)