Intracranial Aneurysms in Sickle-Cell Disease Are Associated With the Hemoglobin SS Genotype But Not With Moyamoya Syndrome

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Background and Purpose—Intracranial aneurysms and aneurysmal subarachnoid hemorrhage may occur more frequently in sickle-cell disease (SCD), and this could be related to the sickle genotype and moyamoya syndrome seen in SCD.

Methods—Records from a total of 1002 patients with SCD attending 2 specialized adult hematologic services were retrospectively reviewed. We analyzed data of a cohort of 767 patients attending 1 SCD clinic between 2002 and 2013 and of 235 patients from the other clinic who had had neurovascular imaging between 2007 and 2014.

Results—We identified 4 patients in the cohort who had an aneurysmal subarachnoid hemorrhage during 9063 patient-years. The highest incidence rate was seen among women in the age group 30 to 39 years with the hemoglobin SS (HbSS) genotype (440 per 100,000 patient-years). Unruptured intracranial aneurysms were found in 20 of the 324 patients, who had imaging data; the prevalence was significantly higher in patients with HbSS genotype compared with other sickle genotypes with the highest prevalence (15%) observed in women in the age group 30 to 39 years. Fifty-one HbSS patients had a moyamoya vasculopathy, but only 3 of these had concomitant intracranial aneurysms.

Conclusions—Intracranial aneurysms are common in HbSS SCD. There was also a trend toward more common occurrence of aneurysmal subarachnoid hemorrhage in HbSS; women in the age group 30 to 39 years were most at risk. There was no correlation between the occurrence of intracranial aneurysms and moyamoya syndrome. (Stroke. 2016;47:1710-1713. DOI: 10.1161/STROKEAHA.116.012664.)

Key Words: anemia, sickle cell ■ intracranial aneurysm ■ moyamoya disease ■ stroke ■ subarachnoid hemorrhage

Sickle-cell disease (SCD) is one of the commonest severe genetic disorders in the United Kingdom and a global health problem. SCD is caused by the presence of hemoglobin S (HbS) in which glutamic acid at position 6 of the β-globin chain of hemoglobin is changed to valine. The disorder encompasses several genotypes—the most common being HbSS (homozygosity for HbS); other genotypes include compound heterozygosity with HbC variant (HbSC) or β-thalassemia (HbSβ thalassemia). Polymerization of deoxygenated HbS leads to distortion of erythrocytes into the classical sickle shape. The sickled erythrocytes cause the 2 major pathological phenomena: chronic hemolytic anemia and recurrent vaso-occlusive pain crises. Acute clinical events are common occurrences in SCD; one of which is stroke.1 Ischemic lesions of the brain are the most common cause of stroke, but hemorrhage may also occur. Some patients develop a cerebral vasculopathy, including stenosis of the supraclinoid carotid arteries causing a moyamoya syndrome. There are several case reports2-4 describing intracranial aneurysms and aneurysmal subarachnoid hemorrhage (SAH) and its management in patients with SCD, which were recently reviewed by Brandão et al.4 However, the prevalence of intracranial aneurysms and incidence of aneurysmal SAH in the sickle-cell population remain unclear; 2 recent publications indicate that intracranial aneurysms are indeed more common in SCD.5,6 Patients with HbSS may be most at risk.7 The present study aimed to investigate whether intracranial aneurysms and aneurysmal SAH are more common in HbSS and to what extent intracranial aneurysms and moyamoya syndrome occur together.

Methods

We studied 2 patient populations; one was a cohort of 767 consecutive patients (337 men) attending an adult sickle-cell clinic at the Department of Haematology at King’s College Hospital (KCH),...
London, United Kingdom, between January 1, 2003, and December 31, 2013. We retrospectively reviewed patient charts from the cohort. Using the hospital’s electronic patient record system, we extracted a subgroup of patients from the cohort on the basis of having had cerebrovascular imaging (computed tomographic angiography or magnetic resonance imaging and magnetic resonance angiography [MRA]) done at any time since electronic patient record system started recording. The electronic patient record is considered robust since 2002. SCD genotypes in our area include HbSS, HbSC, HbSβ thalassemia, HbSβ thalassemia, and HbSHPFH. The catchment area of the Department of Haematology was encompassed in the catchment area of the Department of Neurosurgery at KCH, that is, a patient from the cohort who had an aneurysmal SAH would be admitted to and have brain imaging done at KCH during the study period, which was defined as January 1, 2002, December 31, 2013. As a consequence, it enabled us to calculate an incidence rate for aneurysmal SAH in SCD. We calculated a crude incidence rate for the genotype HbSS and stratified the incidence rate by sex and categorized age as 0 to 29, 30 to 39, 40 to 49, 50 to 59, 60 to 69, 70 to 79, and 80 years or older. Cases of aneurysmal SAH were ascertained by reviewing neurological letters and clinical notes and patient-years summarized in the specific age groups within the study period. The second patient population was a group of 235 adult patients (72 men) with SCD at the Department of Haematology, Guy’s and St. Thomas hospital, London, United Kingdom, who have had magnetic resonance imaging/MRA carried out between January 1, 2007, and December 31, 2014.

MRA was performed on 1.5-T magnets with a 3-dimensional time-of-flight sequence, and in general, scan parameters were repetition time=23.0 ms, flip angle=20°, echo time=3 ms, and slice thickness=1.4 mm. We included patients who have had MRA or computed tomographic angiography, and in both the KCH and Guy’s and St. Thomas hospital, radiology requests and reports were reviewed and information on indication for scan and location and size of intracranial aneurysms, if any, was extracted. The reports were categorized as no aneurysm, possible aneurysm, or definite aneurysm. Possible and definite aneurysms were included in the analysis. Aneurysms were classified as unruptured or ruptured. We also recorded whether the radiology reports mentioned narrowing of the terminal internal carotid artery/arteries or their proximal branches with or without development of collateral small vessels near the apex of the carotid (consistent with moyamoya syndrome). For the calculation of prevalence of intracranial aneurysms, the numerator was the number of patients harboring unruptured intracranial aneurysms and the denominator all patients having had neurovascular imaging for any reason other than a ruptured aneurysm. The prevalence was stratified by sickle genotype, sex, and age groups as above. We compared patients of the HbSS genotype with patients of other SCD genotypes. For statistics, we used the Fisher exact test with significance level P<0.05. All analyses were performed using the OpenEpi software.8

Results

Incidence of Aneurysmal SAH

Within the KCH cohort, 4 patients, all HbSS, had an aneurysmal SAH. Three of the patients were women in the age group 30 to 39 years; 1 patient bled while on holiday abroad, and her neuroimaging was not available for review. The fourth patient was a boy who bled from a 3-mm anterior choroidal artery aneurysm at the age of 12 years. The incidence rate stratified by genotype is shown in Table 1. The crude incidence rate for HbSS patients was 71 per 100000 patient-years. In female HbSS patients in the age group 30 to 39 years, the observed incidence rate was 440 per 100000 patient-years, but when compared with female patients in the same age group of other sickle genotypes, the difference was not significant (P=0.34).

Thirty-eight of the 767 patients died during the observation period. Four deaths were caused by neurovascular disease: two patients died of moyamoya-associated intracerebral hemorrhage, 1 patient died of cerebral infarction, and 1 patient died of acute subdural hematoma. Twenty-five patients died of other specific causes. In 9 patients, we were not able to establish the cause of death, but we are not aware of any patient who died suddenly after experiencing headache, that is, likely to have had aneurysmal SAH.

Unruptured Aneurysms in Patients With Previous Aneurysmal SAH, Including a De Novo Aneurysm

Two of the patients who had an aneurysmal SAH had 1 and 3 additional aneurysms, respectively. A third patient who had a ruptured anterior choroidal artery aneurysm clipped in 2002 developed a left sided hemiparesis 11 years later. Follow-up catheter angiogram in 2005 had shown no other aneurysms. A new magnetic resonance imaging/MRA showed a de novo 9-mm right posterior cerebral artery aneurysm, which was partially thrombosed, causing distortion of the right cerebral peduncle.

Prevalence of Intracranial Aneurysms

Excluding patients having had neurovascular imaging in the course of investigation or follow-up for aneurysmal SAH, a total of 324 patients (89 of the 767 from KCH and 235 from Guy’s and St. Thomas hospital) had neurovascular imaging carried out. Three hundred sixteen of the 324 patients had MRA, whereas 8 patients had computed tomographic angiography. Scans were requested as workup for headache, stroke, seizures, miscellaneous neurological symptoms, abnormal transcranial Doppler screening, and follow-up. Twenty of the 324 patients had incidental intracranial aneurysms; of which, all but one had HbSS. The 1 patient with HbSC had a 2-mm aneurysm originating from the cavernous segment of the left internal carotid artery. Comparing patients who were diagnosed with an intracranial aneurysm and patients without aneurysm, it was found that there was no significant difference between the 2 groups in terms of reasons for scanning (data not shown). Two patients diagnosed with an intracranial aneurysm had also cerebral infaracts; 1 was a patient with coexisting moyamoya vasculopathy (see below). The crude prevalence rate for patients with the HbSS genotype was 8%, which was significantly higher than that for the other sickle-cell genotypes (1%; P<0.05). Table 2 shows the distribution of unruptured intracranial aneurysms in patients with the HbSS genotype stratified by age and sex. The highest prevalence (15%) was observed in women in the age group 30 to 39 years.

Characteristics of Intracranial Aneurysms

A total of 37 aneurysms (unruptured and ruptured) were observed among 24 patients. Nine patients (38%) had >1 aneurysm; of which, 6 patients had 2, 2 had 3, and 1 patient had 4 aneurysms. Twenty-three (62%) and 14 (38%) of the aneurysms were located in the anterior and posterior cerebral circulation, respectively. Sizes of the ruptured aneurysms were 3, 5, and 13 mm, respectively. In the patient who bled abroad, we could not retrieve information about the size of the
aneurysm. Two unruptured aneurysms measured 9 and 8 mm, respectively; the rest measured <7 mm, with 19 aneurysms measuring <3 mm.

Intracranial Aneurysms With Moyamoya Syndrome
Fifty-one of 324 patients (16%) had a moyamoya vasculopathy identified on imaging. In 34 patients, the internal carotid arteries or their proximal branches were narrowed bilaterally. Twenty-nine patients had moyamoya collaterals. In only 3 patients, did the vasculopathy affect the posterior circulation. Thirty-six patients with a moyamoya vasculopathy also had infarcts, 2 had hemorrhages, and 5 had both. Three of the 51 patients had coexisting intracranial aneurysms. Overall, there was no correlation between intracranial aneurysms and moyamoya syndrome (P>0.99). One patient had bilateral aneurysms at the precommunicating segment of the posterior cerebral artery in the setting of bilateral occlusions of the internal carotid arteries and enlarged posterior communicating arteries, suggesting that the aneurysms may have been flow related in that particular case.

Other Findings
In 2 patients, a convexity SAH was found. Neither was caused by a ruptured aneurysm; 1 was in the setting of a moyamoya vasculopathy (see above). Thirty-four patients not diagnosed with an intracranial aneurysm or moyamoya vasculopathy had cerebral infarcts. Among all 35 patients with cerebral infarcts or narrowing of the lumen.

Table 2. Prevalence of Unruptured Intracranial Aneurysms in Female and Male HbSS Patients Stratified by Age

<table>
<thead>
<tr>
<th>Sex</th>
<th>Age Group, y</th>
<th>No. of Patients</th>
<th>Cases</th>
<th>Prevalence, %</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women</td>
<td>0–29</td>
<td>71</td>
<td>5</td>
<td>7</td>
<td>2–16</td>
</tr>
<tr>
<td></td>
<td>30–39</td>
<td>39</td>
<td>6</td>
<td>15</td>
<td>6–31</td>
</tr>
<tr>
<td></td>
<td>40–49</td>
<td>28</td>
<td>3</td>
<td>11</td>
<td>2–28</td>
</tr>
<tr>
<td></td>
<td>50+</td>
<td>10</td>
<td>0</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Men</td>
<td>0–29</td>
<td>60</td>
<td>3</td>
<td>5</td>
<td>1–14</td>
</tr>
<tr>
<td></td>
<td>30–39</td>
<td>18</td>
<td>2</td>
<td>11</td>
<td>1–35</td>
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<td></td>
<td>40–49</td>
<td>14</td>
<td>0</td>
<td>...</td>
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<tr>
<td></td>
<td>50+</td>
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CI indicates confidence interval.

In this retrospective study, we have used available data to add to our knowledge of cerebrovascular complications in SCD. Our study suggests an increased prevalence of intracranial aneurysms in sickle-cell patients with the HbSS genotype compared with other sickle genotypes and possibly an increased incidence of aneurysmal SAH. If we assume that non-HbSS genotypes do not confer a protective effect, then our data indicate that intracranial aneurysms and aneurysmal SAH are more common in SCD of the genotype HbSS than in the background population. Our data also give an estimate of the incidence of aneurysmal SAH in SCD.

The crude prevalence estimate is comparable with findings of other recent studies. Nabavizadeh et al. found 19 patients harboring aneurysms in a study of 598 children and 111 adults with SCD. Twelve of the 19 patients were adults, thus suggesting a prevalence of 10.8% among adult patients. Saini et al. found a prevalence of 2.8% in a pediatric population with SCD. Incidence of aneurysmal SAH (and probably also prevalence of intracranial aneurysms) varies by race and ethnicity; black Americans have a higher incidence of aneurysmal SAH than white Americans. Thus, when comparing incidence and prevalence data in patients with SCD with those in other populations, only part of the difference may be attributable to SCD per se.

We confirmed previous findings of an increased proportion of patients with multiple aneurysms. In the general population, it is estimated that 20% of cases have multiple aneurysms. We also found a higher propensity for a location in the posterior circulation as noted previously (for comparison, in the general population, an often quoted figure is 8% from the International Cooperative Study on the Timing of Aneurysm Surgery). The reason for this remains obscure. We speculated that a moyamoya vasculopathy affecting the internal carotid arteries could cause redistribution of blood flow and in turn predispose to flow-related posterior circulation aneurysms, but this does not seem to be the case. There was no correlation between intracranial aneurysms and moyamoya vasculopathy, suggesting that moyamoya syndrome and intracranial aneurysms may be the result of 2 different pathobiological processes. Oyesiku et al. proposed in 1991 that the adhesion of the sickled erythrocyte to the endothelial cell initiates 2 opposing processes, 1 being degeneration of the vessel wall, leading to hemorrhage or aneurysm formation, whereas the other being a reparative process that may lead to infarcts or narrowing of the lumen.

The increased prevalence of intracranial aneurysms found in this retrospective study makes a case for a prospective study of screening patients with SCD for intracranial aneurysms. Most unruptured intracranial aneurysms were, however, small. This raises an important clinical question: how to manage a small aneurysm found incidentally in a patient with SCD? Estimation of rupture risk is often based on the location and size of the aneurysm and on whether the patient previously has had an SAH from a separate aneurysm. From
the International Study of Unruptured Intracranial Aneurysm, the rupture risk from small (<7 mm) aneurysms in patients without a previous aneurysmal SAH is estimated at 0.1% per year, which is considered a low risk. In this study, 2 ruptured aneurysms were 3 and 5 mm. It has been suggested that small aneurysms in patients with SCD are more prone to rupture than in the general population. An alternative explanation could be that as most aneurysms are small, ruptured small aneurysms are seen with regularity although the rupture risk is low for the individual aneurysm. For aneurysms <3 mm, it would be reasonable to do interval magnetic resonance imaging/MRA with a view to assess aneurysm growth, if any. Most importantly, any sudden onset headache in a patient with SCD should be investigated on the suspicion of an aneurysmal SAH.

The strength of the study includes the stratification by sex and age, as well as providing a comparable control group in terms of race and ethnicity. There are also some limitations: first, only one fourth of the total number of patients followed up in the 2 clinics had neurovascular imaging. These investigations were done for various neurological symptoms, and the practice differed between the clinics, reflected in the wide difference in the proportion of patients having imaging. This raises concern for a selection bias. Scans were, however, requested with a low index of suspicion, and most scans were normal. The reason for scanning did not differ between those who were diagnosed with an intracranial aneurysm and those who were not. In general, small unruptured aneurysms are considered asymptomatic, and as we excluded patients with previous SAH from a separate aneurysm from the analysis, the bias is most likely minor. Furthermore, we did not find an association with moyamoya syndrome, and intracranial aneurysms are not likely to be associated with any other condition that would cause neurological symptoms. The bias does not favor one or the other genotype and is unlikely to influence on the main conclusions of the study. Second, in 9 cases, we could not establish the cause of death, and thus, we may have missed cases of aneurysmal SAH. Third, patients in the cohort were not necessarily followed up in the clinic during the entire observation period, and this may have led to an underestimation of the incidence rate. Fourth, patients with aneurysms seen on MRA generally did not have a subsequent catheter angiogram to confirm the findings. Saini et al found that many aneurysms seen on catheter angiogram were missed on MRA, indicating that we may have underestimated the true prevalence. On the other hand, we chose to pool definite and probable aneurysms in the analysis. Fifth, current transfusion programs for primary and secondary prevention of cerebrovascular disease in SCD may alter the natural history of intracranial aneurysms too.

Conclusions
Intracranial aneurysms are common in HbSS SCD. There was also a trend toward more common occurrence of aneurysmal SAH in HbSS; women in the age group 30 to 39 years were most at risk. There was no correlation between the occurrence of intracranial aneurysms and moyamoya syndrome.

Disclosures
None.

References
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