First Ischemic Stroke in Sickle-Cell Disease
Are There Any Adult Specificities?

David Calvet, PhD; Françoise Bernaudin, MD*; Antoine Gueguen, MD*;
Hassan Hosseini, PhD; Anoosha Habibi, MD; Frédéric Galactéros, PhD; Pablo Bartolucci, PhD

Background and Purpose—There is little evidence about characteristics of ischemic stroke (IS) occurring in adults with sickle-cell disease (SCD). The objective of this study was to assess characteristics of first-ever IS in adults with SCD and to assess whether they differ from those occurring in child patients with SCD.

Methods—Adult and child individuals with SCD who had a first-ever IS were identified from cohorts of patients followed up in an adult and a child sickle cell referral center. Mechanisms of IS were determined by consensus meeting from all available explorations using the following predefined classification: Vasculopathy, cardioembolism, other defined cause, and undetermined. Treatment and stroke recurrences were recorded from prospective follow-up performed in the referral centers.

Results—Twenty-nine adults and 26 children had a first-ever IS; mean age (SD) was 7.1 (4.3) and 32.3 (11.6), respectively. With regard to IS mechanism, vasculopathy was less often the cause of IS in adults (12/29, 41%) than in children (24/26, 92%; P<0.001). Other causes of IS in adults were cardioembolism in 7, antiphospholipid syndrome in 1, toxic (cocaine) in 1, and undetermined in 8. Adults with SCD had a higher risk of recurrent stroke (23.1% [7.0–39.2] at 5 years) compared with children (1 recurrence only; P log rank=0.046) despite exchange-blood transfusion in patients with vasculopathy.

Conclusions—First-ever IS occurring in adults with SCD has specificities that justify further studies conducted in adults with SCD to improve understanding and management. (Stroke. 2015;46:2315-2317. DOI: 10.1161/STROKEAHA.115.010153.)

Key Words: adult ■ anemia, sickle cell ■ child ■ follow-up studies ■ stroke

Stroke is one of the leading causes of death in both children1 and adults2 with sickle-cell disease (SCD). Ischemic stroke (IS) subtypes vary, but the most common subtype of overt cerebral infarction is border-zone infarcts that occur between the anterior cerebral artery and middle cerebral artery related to a specific large-vessel vasculopathy.3 Because of the paucity of data dedicated to IS in adults and that IS in adults are commonly recurrences of strokes that happened during childhood, SCD adults with IS are most often managed as children are, even in occurrence of a first IS.

The objective of this study was to assess characteristics of a first-ever IS in adults with SCD and to assess whether they differ from those occurring in child patients with SCD in terms of underlying mechanism and risk of recurrences. Then, we report the characteristics of 29 first-ever IS occurred in adult patients with SCD compared with 26 IS occurred during childhood.

Methods

SCD children and adults with a first-ever IS were identified from our prospective cohorts of patients followed up in our pediatric and adult referral centers, as previously described.4,5 Follow-up was done prospectively in the referral center where patients were examined at least twice a year.

A consensus meeting was held with a neurologist, an internist, a pediatrician when appropriate, and a neuroradiologist to assess the likely cause of stroke according to the following predefined classification: vasculopathy, cardioembolism, other defined cause, and undetermined as previously described.6

The study was conducted in accordance with the provisions of the Declaration of Helsinki and French Law and regulations.

Statistical Analysis

Data were expressed as mean (SD), median with interquartile range, or percentage, as appropriate. Kaplan–Meier survival analysis was used to assess the cumulative risk of recurrent stroke. The predictive value of the stroke period (adulthood) with respect to the occurrence of recurrent IS during follow-up was assessed with the use of Log-rank tests.

Results

From 1985 to 2014, among 2620 adults with SCD routinely followed up in our adult center, 29 had a first-ever IS when they
were ≥18-year-old, 2 being fatal. Twenty-five were homozygous, 3 were SC, and 1 was S-β0 thalassemia. Mean (SD) age at the time of stroke was 32.3 years (11.6); 15 (52%) were men, and 5 had high systolic blood pressure. From 1985 to 2014, among a cohort of 510 children with SCD followed up in our child center, 26 children with SCD, all being homozygous, had a first IS, of which 3 in the newborn cohort early screened by transcranial Doppler, whereas the 23 others were referred to a first IS, of which 3 in the newborn cohort early screened by transcranial Doppler, whereas lactate dehydrogenase did not differ (data not shown). Among the 12 adults with vasculopathy, 6 had Moyamoya syndrome and 2 had an extracranial vasculopathy, associated with an intracranial vasculopathy in 1. Other causes of IS in adults were (1) cardioembolism in 7, corresponding to systolic dysfunction in 2, complicated by atrial fibrillation in 1, large patent foramen ovale in 3, with fat embolism in 1, dilated cardiomyopathy in 1, and a prosthetic valve with insufficient anticoagulation in 1; (2) antiphospholipid syndrome in 1; (3) toxic (cocaine) in 1, and (4) undetermined in 8. At the time of their stroke, 1 adult had a known vasculopathy and was treated by EBT. Among adults with biological data before treatment and IS, the hemoglobin level was lower in patients with vasculopathy than in patients without, whereas lactate dehydrogenase did not differ (data not shown). Among the newborn cohort, one IS occurred just before the confirmatory abnormal transcranial Doppler, another one in a child with no available temporal window but severe vasculopathy and the last one after an acute chest syndrome in a child with no vasculopathy. The remaining 23 children with a vasculopathy-related IS were referred to the center after the first IS occurrence. All children with IS were treated by EBT, and 12 of them were transplanted with a genoidentical donor. Mean (SD) age at the time of stroke was 7.1 years (4.3), and 8 (31%) were men.

In adults, diagnostic and etiologic work-up included brain imaging in all (magnetic resonance imaging in 83%), arterial work-up in all (magnetic resonance angiogram in 79%), and echocardiography in 76% (transesophageal echocardiography in 62%). With regard to IS mechanism, vasculopathy was less often the cause of stroke in adults (12/29, 41%) than in children (24/26, 92%; P<0.001). Among the 12 adults with vasculopathy, 6 had Moyamoya syndrome and 2 had an extracranial vasculopathy, associated with an intracranial vasculopathy in 1. Other causes of IS in adults were (1) cardioembolism in 7, corresponding to systolic dysfunction in 2, complicated by atrial fibrillation in 1, large patent foramen ovale in 3, with fat embolism in 1, dilated cardiomyopathy in 1, and a prosthetic valve with insufficient anticoagulation in 1; (2) antiphospholipid syndrome in 1; (3) toxic (cocaine) in 1, and (4) undetermined in 8. At the time of their stroke, 1 adult had a known vasculopathy and was treated by EBT. Among adults with biological data before treatment and IS, the hemoglobin level was lower in patients with vasculopathy than in patients without, whereas lactate dehydrogenase did not differ (data not shown). Among the newborn cohort, one IS occurred just before the confirmatory abnormal transcranial Doppler, another one in a child with no available temporal window but severe vasculopathy and the last one after an acute chest syndrome in a child with no vasculopathy. The remaining 23 children with a vasculopathy-related IS were referred to the center after the first IS occurrence. All children with IS were treated by EBT, and 12 of them were transplanted with a genoidentical donor.

Mean (SD) follow-up in adults was 7.2 years (6.3) and 8.8 (4.6) years in children. Adults with SCD had a higher risk of recurrent stroke than children (P log rank=0.046).

Table shows characteristics of adult patients with recurrent stroke during follow-up. In adults, the absolute risk of recurrent stroke was 16.0% (95% confidence interval, 1.7–30.3) at 2 years and 23.1% (7.0–39.2) at 5 years. During follow-up, only one child experienced a recurrent stroke that was hemorrhagic and fatal 11.3 years after the initial IS related to vasculopathy.

### Discussion

Our study shows that first-ever IS in adults with SCD have wider variety of causes and have a higher risk or recurrence than those occurring in children.

It was well showed that transfusion therapy decreases dramatically the risk of a first IS in child with increased blood-flow velocities identified by Doppler. It was also suggested in children that EBT could be useful in secondary prevention. By contrast to children, in our study, IS recurrences were observed in adults with vasculopathy despite treatment with EBT (Table). It was suggested that IS in adults could be related to more severe vasculopathy, in particular, in the case of Moyamoya syndrome. However, in our study, among 12 patients with a first-ever vasculopathy-related IS, 4 had recurrences, of which 3 occurred in patients without Moyamoya syndrome. Systematic magnetic resonance imaging to detect not only vasculopathy but also silent cerebral infarcts could be important in adults to identify those at high risk of a first-ever IS.

Our findings also emphasize the need for a detailed etiologic work-up in all adults with SCD who had an IS, including a detailed cardiac work-up as cardiopathy is not unusual in patients with SCD.

First IS occurring in adults with SCD has some specificities that do not allow to simply derive management from pediatric practice, and further studies dedicated to adults are needed to improve our knowledge of stroke occurring in adults with SCD.

### Table. Characteristics of Adult Patients With Recurrent Stroke During Follow-Up

<table>
<thead>
<tr>
<th>Age at the Time of IS, y</th>
<th>Sex</th>
<th>Genotype</th>
<th>Cause of IS</th>
<th>Details</th>
<th>Exchange-Blood Transfusion After IS</th>
<th>Time From IS to Recurrence, y</th>
<th>Cause of Recurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td>35</td>
<td>M</td>
<td>SS</td>
<td>Vasculopathy</td>
<td>Intra and extracranial</td>
<td>Yes</td>
<td>1.6</td>
<td>Vasculopathy</td>
</tr>
<tr>
<td>43</td>
<td>F</td>
<td>SS</td>
<td>Unknown</td>
<td>...</td>
<td>No</td>
<td>22.0</td>
<td>Unknown</td>
</tr>
<tr>
<td>34</td>
<td>F</td>
<td>SS</td>
<td>Vasculopathy</td>
<td>With Moyamoya syndrome</td>
<td>Yes</td>
<td>1.4</td>
<td>Vasculopathy*</td>
</tr>
<tr>
<td>47</td>
<td>M</td>
<td>SS</td>
<td>Cardioembolic</td>
<td>...</td>
<td>No</td>
<td>6.1</td>
<td>Cardioembolic</td>
</tr>
<tr>
<td>19</td>
<td>M</td>
<td>SS</td>
<td>Cardioembolic</td>
<td>...</td>
<td>No</td>
<td>2.0</td>
<td>Cardioembolic</td>
</tr>
<tr>
<td>45</td>
<td>F</td>
<td>SC</td>
<td>Unknown</td>
<td>...</td>
<td>No</td>
<td>13.3</td>
<td>Cardioembolic</td>
</tr>
<tr>
<td>21</td>
<td>M</td>
<td>SS</td>
<td>Cardioembolic</td>
<td>...</td>
<td>No</td>
<td>3.3</td>
<td>Cardioembolic</td>
</tr>
<tr>
<td>23</td>
<td>F</td>
<td>SS</td>
<td>Vasculopathy</td>
<td>...</td>
<td>Yes</td>
<td>0.9</td>
<td>Vasculopathy</td>
</tr>
<tr>
<td>24</td>
<td>F</td>
<td>SS</td>
<td>Vasculopathy</td>
<td>Extracranial vasculopathy</td>
<td>Yes</td>
<td>1.7</td>
<td>Vasculopathy</td>
</tr>
</tbody>
</table>

F indicates female; IS, ischemic stroke; and M, male.

*Recurrent stroke was hemorrhagic.
Disclosures
None.

References
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