CASE REPORT

The cause of the stroke: a diagnostic uncertainty

Abhishek Dattani,¹ Ava Jackson²

¹Stroke Medicine, Barts Health NHS Trust, London, UK
²Stroke and Geriatric Medicine, Barts Health NHS Trust, London, UK

Correspondence to
 Dr Abhishek Dattani,
 a.dattani07@gmail.com

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SUMMARY

A 39-year-old man with a history of sickle cell disease (SCD) presented with left leg weakness. He had a normal CT head and CT angiogram, but MRI head showed multiple acute bilateral cortical infarcts including in the right precentral gyrus. The MRI findings were more in keeping with an embolic source rather than stroke related to SCD, although it could not be ruled out. He also had an echocardiogram which revealed a patent foramen ovale. He was treated with antiplatelet therapy and also had red blood cell exchange transfusion. His symptoms improved significantly and he was discharged with follow-up as an outpatient and a cardiology review.

BACKGROUND

Stroke in sickle cell disease (SCD) is managed very differently in comparison to other types of strokes. This case report demonstrates the management of these types of stroke but also brings in the element of doubt over the cause of a stroke in this patient due to his MRI and echocardiogram findings.

CASE PRESENTATION

A 39-year-old man with known SCD of HbSS genotype presented to the Accident & Emergency department during the night with sudden-onset left leg weakness that began that morning. He explained that he woke up well in the morning but later developed numbness in the left leg which was followed by weakness. The numbness had settled but the weakness persisted. He had no speech or visual disturbance, no headache, no vomiting or dizziness and no back pain. He had a medical history of SCD diagnosed at a young age, with two previous chest crises and last admission in 2012 with an uncomplicated sickle crisis. He had no history of stroke or transient ischaemic attack but did have a history of hepatitis B infection, avascular necrosis of the right femoral head and previous blood transfusion in Nigeria 20 years ago. He had no other vascular risk factors. His regular medications included folic acid, penicillin V and naproxen.

On examination, his observations were normal. He had a regular pulse and a clear chest with normal heart sounds. His abdomen was soft and non-tender and he had no calf swelling or tenderness. Neurological examination revealed normal cranial nerve examination. On peripheral nerve examination, he had no wasting/fasciculations, normal tone and normal upper limb examination. Lower limb examination revealed a normal right lower limb but weakness in the left lower limb graded 3/5 hip flexion, 4/5 hip extension, 3/5 knee flexion and

extension and 2/5 ankle dorsiflexion and plantar-flexion. He had a downgoing right plantar reflex and an equivocal left plantar reflex. His sensation was normal and he had no limb ataxia. He had a positive Hoover's test, however, and his neurology was showing significant improvement on further assessment. The patient's National Institutes of Health Stroke Scale score was 1 on presentation and he had a normal ECG.

INVESTIGATIONS

His blood tests on admission showed a haemoglobin (Hb) level of 97 with a HbS of 87.4%, Hb F 4.0% and HbA 2.2%. A CT head showed no acute infarct and no intra or extra-axial haemorrhage. There was an area of mature ischaemic change in the left centrum semiovale extending into the cortex of the left precentral gyrus. He had a CT angiogram which showed normal intracranial and extracranial vessels.

MRI head (figures 1–4) showed acute bilateral cortical infarcts in different arterial territories with some established ischaemic change. There was diffusion restriction involving the right precentral gyrus in keeping with the patient's presentation. The multiple territories, however, suggested an embolic source or a patent foramen ovale (PFO). He had an echocardiogram which showed normal left ventricle and right ventricle with good systolic function. Bubble study (figures 5 and 6) showed numerous bubbles crossing from the right to left heart with release of Valsalva suggesting the presence of a PFO. Deep vein thrombosis (DVT) was ruled out on ultrasound Doppler imaging of both legs.

DIFFERENTIAL DIAGNOSIS

Given that the risk of stroke in patients with SCD is higher, it was important for the patient to be evaluated in the hyper-acute stroke unit (HASU) for further assessment and an MRI head with diffusion-weighted imaging.

Once an ischaemic event was confirmed on the MRI scan, the next step was to decide whether the stroke was due to SCD and this was a very difficult decision to make. The MRI findings were compatible with an embolic source rather than SCD. He did, however, have a high sickle percentage of 87.4.

His echocardiogram findings of a PFO added further doubt over the SCD causing the stroke, but it should be noted that PFOs are found in a significant proportion of the normal population and may be an incidental finding.

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Figure 1 MRI imaging showing bilateral cortical infarcts.

TREATMENT

He was treated with antiplatelet therapy and a statin. His case was thoroughly discussed between the stroke, neuroradiology and haematology consultants and it was decided that he should have a red cell exchange transfusion as it was difficult to rule out SCD as the cause of the stroke. He went on to have the exchange transfusion without complications. His HbS percentage after exchange transfusion was 23.5.

OUTCOME AND FOLLOW-UP

This patient made a good recovery with significant improvement in his weakness during his stay in hospital and was discharged with follow-up. His blood tests at the time of the stroke included a young stroke screen which was negative including antinuclear antibodies, antineutrophil cytoplasmic antibody and anticardiolipin antibodies. His most recent review in the stroke clinic 5 months after presentation showed good improvement and no

Figure 2 MRI imaging showing bilateral cortical infarcts.

evidence of recurrence of stroke. He remains on clopidogrel and continues to have regular exchange transfusions with the haematology team without any complications. His most recent postexchange transfusion HbS percentage was 25.0.

DISCUSSION

Medical management of strokes has drastically changed in the UK with the introduction of HASU which is the ideal site of management of patients who are having acute cerebrovascular accidents.¹ The National Clinical Guideline for Stroke states that all patients with features suggesting an acute stroke should receive urgent brain imaging which would include either CT or diffusion-weighted MRI.² Patients with features that have resolved by the time of presentation, and therefore may have had a transient ischaemic attack, should be assessed by a stroke specialist urgently. Patients should also have carotid artery imaging with either ultrasound or CT angiogram. Acute stroke is a medical emergency and the initial management of acute ischaemic stroke would include the use of recombinant tissue plasminogen activator ideally within 4.5 hours of onset of symptoms³ followed by antiplatelet therapy if there has been no haemorrhagic transformation.

Stroke is more common in patients with SCD compared with the general population with prevalence thought to be around 3.75%, although this varies based on the sickle cell genotype.⁴ The pathophysiology of stroke in SCD is thought to be different. The initial theory of the cause of stroke in SCD was an increase in blood viscosity due to sickled red cells which causes stasis and ischaemia leading to a stroke. There are, however, further factors that play a role including the attachment of red blood cells to the vascular endothelium leading to the activation of a pro-inflammatory state causing hyperplasia and fibrosis, and eventually, thrombosis. Furthermore, research suggests a role of the lack of L-arginine in patients with SCD, which leads to a reduction in the effectiveness of nitric oxide-mediated vasodilation pathways.⁵ On the other hand, a study in 2015 has shown that first ischaemic strokes in adult patients with SCD were less likely to be secondary to vasculopathy in comparison to children (41% vs 92%) and were more likely to be cardioembolic or due to other causes such as antiphospholipid syndrome, cocaine use or other unknown causes.⁶

Patients with SCD are at increased risk of ischaemic strokes and are also at a greater risk of haemorrhagic stroke in comparison to the general population with the greatest incidence being in the 20–29 age group (440 per 100 000 person-years vs 14 per 100 000 person-years in non-SCD). A few studies have been done to look at the risk factors associated with a haemorrhagic stroke in the SCD population and these appear to be recent blood transfusion, hypertension, coagulopathy, recent steroid treatment or acute chest crisis.⁷

As with patients without SCD, it is important to perform rapid investigations for patients with SCD who present with symptoms suggestive of a stroke. Initial investigations include CT or MRI brain, although CT may miss early infarcts but is very sensitive for haemorrhagic strokes. It is recommended that vascular imaging, using either CT angiography or MRI angiography, be performed in patients with SCD who present with a stroke to evaluate the cerebral vasculature as well as extracranial disease. These imaging modalities also help to diagnose conditions such as Moyamoya which is a complication in SCD. In cases of subarachnoid haemorrhage, cerebral angiography can be used to evaluate cerebral aneurysms but in patients with SCD, this can increase risk of stroke and therefore it is recommended

Figure 3 Diffusion restriction suggesting acute ischaemia.

that they receive adequate hydration and exchange transfusion to maintain a HbS < 30%.⁷

Management of ischaemic stroke in SCD differs significantly from patients with non-SCD. Initial management includes oxygen supplementation to maintain peripheral oxygen saturations above 95% to prevent sickling due to deoxygenation. Thrombolysis has not been well studied in this population group and its use in acute ischaemic stroke in patients with SCD is debated.⁸ Although there appears to be no specific contraindications against its use, it is known that patients with SCD have an increased risk of intracranial haemorrhage and this should be considered before the use of such agents.⁷ The use of red blood cell exchange transfusion is recommended as it decreases HbS concentration, which cause the procoagulant and adhesive properties as well as maximising the delivery of oxygen and thereby decreasing vaso-occlusion.⁹ A post-transfusion target usually consists of a Hb level of above 10 g/dL and HbS percentage of less than 30%.⁴ A retrospective study showed a fivefold decrease in recurrent stroke if exchange transfusion was done within 24 hours of symptom onset.¹⁰ The chronic management and

secondary prevention of stroke in these patients is mainly with chronic exchange transfusions usually at 3–4 week intervals to maintain a HbS percentage of under 30. Although there are clear benefits of exchange transfusions, they do not come without their risks and complications including alloimmunisation, haemolytic transfusion reactions and infection.¹¹ In our patient, there was a long discussion between the stroke, haematology and neuroradiology teams before a decision was made regarding exchange transfusions due to the risks involved. It was decided to commence exchange transfusions given his significantly raised HbS percentage and the findings of the MRI. Besides exchange transfusions, there is also further research looking at the use of hydroxyurea in patients with SCD who have had a stroke, although so far non-inferiority of hydroxyurea in comparison to exchange transfusions has been shown in primary prevention of stroke in patients with SCD.¹²

In terms of management of patients with haemorrhagic strokes in patients with SCD, there is currently very little research. The current recommendation is to follow usual management for the general population including management of coagulopathy,

Figure 4 Diffusion restriction suggesting acute ischaemia.

Figure 5 Four-chamber views of bubble study showing bubbles crossing from the right atrium to left atrium across a patent foramen ovale.

transfer to the intensive care unit and good blood pressure control. As with ischaemic stroke, it is also recommended that exchange transfusion be carried out to maintain HbS percentage below 30, although there appears to be very little research into whether this is beneficial.⁷ Surgical intervention is rarely needed as shown by the STITCH trial which found no significant difference in outcomes between early neurosurgery and medical management although this was done in a non-SCD population.¹³

A PFO has been demonstrated in 10%–26% of healthy adults.¹⁴ In young patients who have had a cryptogenic stroke, however, the prevalence is thought to be much higher, for example, 40% in one study.¹⁵ It is thought that a PFO allows microemboli to pass into the systemic circulation leading to a stroke. Currently, medical management is the first choice of treatment with regard to a PFO following a stroke. This usually consists of antiplatelet therapy or in some cases anticoagulation with warfarin. The main study to look at whether antiplatelet therapy or anticoagulation should be used was the PICSS trial which showed no significant difference in primary end points between the aspirin group compared with the warfarin group.¹⁶

Figure 6 Four-chamber views of bubble study showing bubbles crossing from the right atrium to left atrium across a patent foramen ovale.

Rarely, percutaneous therapy can be used to close the PFO but this is not usual practice. Meta-analysis has shown that this could reduce the risk of recurrent stroke by 86%.¹⁷ On the other hand, a randomised trial consisting of 909 patients comparing medical therapy with closure of PFO showed no significant difference in primary end point (6.8% vs 5.5%, $p=0.37$)¹⁸ and many centres currently choose not to close PFOs in such patients.

Our patient had SCD and a PFO. There is evidence that SCD increases the risk of venous thromboembolisms due to a hyper-coagulable state and patients with SCD have a higher rate of DVT.¹⁹ This raises the question of the stroke in our patient having been caused by microemboli passing into the arterial circulation through his PFO. The management of such patients is debatable and it is difficult to decide whether our patient's stroke was caused by SCD alone or a combination of SCD and the PFO. The answer to this question is relevant beyond academic purposes as the patient would require long-term exchange transfusions if we feel the stroke was caused by his SCD. If, however, the PFO was a leading contribution, then he may not require long-term exchange transfusions and his ideal management would be medical management of stroke prevention. Indeed, there are currently limited studies looking into the management of stroke in patients with both SCD and a PFO and there needs to be more research to look at the long-term outcomes in such patients.

Learning points

- Stroke is common in patients with sickle cell disease (SCD).
- The management of stroke in SCD differs significantly.
- Patent foramen ovale (PFO) provides thromboemboli an access to the systemic circulation to cause stroke in young patients.
- Management of stroke in patients with sickle cell disease and PFO provides further debate and needs more research.

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