CASE REPORT

Subarachnoid haemorrhage and cerebral vasculopathy in a child with sickle cell anaemia

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SUMMARY

Stroke in sickle cell anaemia (SCA) is either infarctive or haemorrhagic in nature. In childhood, over 75% of strokes in SCA are infarctive. We present an adolescent with SCA who developed hypertension at the age of 13, and was treated with lisinopril. Sixteen months later she was found in cardiorespiratory arrest and died on arrival in hospital. The last transcranial Doppler scan performed 6 months before her death and a brain MRI were reported normal. The autopsy discovered massive subarachnoid haemorrhage in association with vascular damage in the circle of Willis arteries. The case highlights a cause of haemorrhagic stroke, the first reported association between hypertension, SCA and a histopathologically proven cerebral vasculopathy. The difficulties in the management of haemorrhagic stroke and the poor outcome in SCA are discussed.

BACKGROUND

Sickle cell anaemia (SCA) is an inherited disorder of the haemoglobin resulting in the development of abnormal haemoglobin polymers in a deoxygenated state, leading to vascular occlusion and cerebrovascular disorders including stroke.

Stroke causes substantial morbidity in children with SCA.¹ Infarction represents the most common cerebrovascular accident (CVA) in childhood; whereas haemorrhagic stroke occurs predominantly in young adults with a peak age of 30 years.² Furthermore, it is one of the most devastating neurological complications of SCA as death occurs in 25–50% of patients within 2 weeks of the haemorrhagic event.²

The cause of haemorrhagic stroke in sickle cell disease is largely undetermined in the majority of cases. In adults, it most commonly results from a ruptured aneurysm,² however, in children this has never been reported. Only a few proposed associated risk factors for haemorrhagic stroke have been rigorously evaluated and none exclusively in children. The patient's age, a low-level steady-state of haemoglobin concentration and high steady-state leucocyte count are the three documented risk factors for children and adults with sickle cell disease.² However, other risk factors, such as previous ischaemic stroke, moyamoya, cerebral aneurysms, acute chest syndrome, acute hypertension and hypertransfusion have also been reported^{3–7} in a small series of case reports. In SCA the association of cerebral vasculopathy with risk of infarctive stroke is well known, but to date no correlation with haemorrhagic stroke has been described.

To the best of our knowledge, this is the first reported association between massive and fatal isolated subarachnoid haemorrhage and cerebral vasculopathy in a paediatric patient with SCA.

CASE PRESENTATION

We present the case of a 15-year-old girl with SCA diagnosed in the first year because of jaundice and bone pains and a positive maternal history of the disorder. In the early years of childhood she was hospitalised for bone pain crises but, apart from nocturnal enuresis, which was treated with desmopressin (DDAVP) at the age of 7 years, she was well. At the age of 13 years she was admitted with abdominal pain and found to be hypertensive (blood pressure (BP) 138/70 mm Hg).

INVESTIGATIONS

A 24 h ambulatory BP profile confirmed systolic hypertension associated with loss of nocturnal systolic dipping status. Clinic BP measurements ranged 128–138 mm Hg (systolic) and 72–82 mm Hg (diastolic) on repeated assessments. Formal measurement of the urine protein level was recorded as spot protein/creatinine ratio at 65 mg/mmol. An in-test glomerular filtration was 177 mL/min/1.73 m², which is consistent with hyperfiltration in SCA. In addition, there was microscopic haematuria and a weakly positive IgG antinuclear antibodies titre. Complement levels were normal with no other abnormalities involving soluble immunology. A previous renal ultrasound scan showed two large kidneys (right 12.2 cm and left 11.4 cm) but was otherwise normal. A 24 h urine sodium excretion was 165 mmol on a 1684 mL urine collection. Lipid profile was normal. Random blood glucose was normal although the patient's glycated haemoglobin levels were below the normal range. It was decided that a percutaneous renal biopsy would not alter the management and therefore it was abandoned. The last transcranial Doppler scan (TCD) was performed 6 months before her death and a brain MRI including a full MR angiography (MRA) according to a research protocol (Silent Infarct Transfusion Trial-SITT) 6 months earlier was reported to be entirely normal. The coagulation screen performed was normal.

TREATMENT

An ACE inhibitor (lisinopril) was initially prescribed but later changed to amlodipine when elevated levels of renin and aldosterone were initially found. However, a repeat test was normal and the patient was put back on lisinopril. Her last

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recorded BP was 107/60 (just below the 50th centile for her age and height).

OUTCOME AND FOLLOW-UP

Unexpectedly, without any pre-existing symptoms, she was found at home in cardiorespiratory arrest. She underwent over 1 h of active cardiopulmonary resuscitation before being certified dead.

The autopsy showed a small spleen (48 g) in keeping with SCA, an enlarged heart (303 g=0.6% of total body weight, normal up to 0.5%) and massive subarachnoid haemorrhage. There was neither intracerebral haemorrhage nor infarction. Grossly, the circle of Willis arteries appeared normal; but embedding them whole for histology demonstrated, amid the lengths of normal artery, a foci of medial and intimal thickening with degeneration of the elastic, and a nearby foci of severe degeneration and attenuation of the artery wall (figures 1 and 2). Aneurysmal dilation had not taken place in the latter areas, and there was no vasculitis.

DISCUSSION

Haemorrhagic strokes differ from ischaemic strokes in many respects, such as natural history, incidence rate, age of the highest incidence, standard screening test, etc. The cause of haemorrhagic stroke in SCA children is largely undetermined in the majority of cases. In a retrospective case-control study, hypertension, corticosteroid drugs, blood transfusion in the past 14 days, non-steroidal anti-inflammatory drugs and coagulopathy were identified as risk factors for haemorrhagic stroke in children with SCA. Only one of the nine haemorrhagic cases evaluated was found to have an aneurysm as a cause for haemorrhage.⁸ This suggests that the cause of haemorrhagic stroke in children is different from that in adults, in whom a ruptured aneurysm is the most commonly identified cause.⁹

In our patient, the histopathology of the cerebral vessels demonstrated coexistence of (A) the stenosing mediointimal thickening, typically identified by TCD and regarded as the precursor to an ischaemic stroke, with (B) the non-aneurysmal mural attenuation and loss of elastic lamina where the leak took place causing the subarachnoid haemorrhage. The pathogenesis of these lesions is presumably the chronic impact of sickled red cells and possibly haemolysis on endothelial cells, which results in the two distinct patterns of pathological damage. Hypertension was the only recognised clinical risk factor for haemorrhagic stroke in our patient and cerebral vasculopathy was reported in the autopsy. Steen *et al*¹⁰ have reported a causal relationship between small vessel disease and brain injury in

Figure 1 Subarachnoid haemorrhage.

Circle of Willis histopathology

Figure 2 Circle of Willis arteries: normal arteries are seen as well as arteries with colocalized mediointimal thickening and attenuation, both associated with disappearance of the elastic lamina; Elastic van Gieson.

SCA. However, no such relationship between vasculopathy and haemorrhagic stroke in patients with SCA has been described pathologically to date.

So far, the association between hypertension and haemorrhagic/ischaemic stroke in SCA in children and adults is not yet proven. However, a review of discharge data in California found a stronger association between hypertension and haemorrhagic CVA rather than ischaemic stroke.¹¹ It is proposed that intermittent hypertension may be a stronger risk factor for haemorrhage stroke⁸ than sustained hypertension. This case highlights the possible association between intermittent hypertension and haemorrhagic stroke, noting the patient's poor compliance with therapy and the presence of intermittent hypertensive peaks during follow-up. Intermittent hypertension seems to be an important risk factor for haemorrhagic stroke and not an after effect of it. The risk of infarctive stroke increased with systolic but not diastolic BP as shown in the report of Cooperative Study of Sickle Cell Disease (CSSCD) BP measurements from patients ≥ 2 years of age with SCA. In this study neither systolic nor diastolic pressures were significant predictors of haemorrhagic stroke even though the sample was small (only 26 were reported).¹² Presently available evidence on the relationship between hypertension and haemorrhagic stroke in children is conflicting.

This case raises important questions about the management of hypertension in patients with SCA. BP values that may be considered normal or representing only mild hypertension in normal individuals must be viewed as high risk in SCA, although the impact on morbidity and mortality is not completely known. Some authors suggest early treatment for mild to moderately raised BP in SCA.¹³ The second important issue raised by our case concerns the role of MRA, MRI and TCD in predicting haemorrhagic stroke in SCA. These neuroimaging studies contribute to the standard screening for infarctive stroke in SCA, even though the STOP study did not specifically differentiate TCD results between ischaemic and haemorrhagic stroke. This is confirmation of the fact that intracranial haemorrhage is less clearly predicted by TCD than ischaemic stroke.¹⁴ The definition of haemorrhagic stroke is quite broad and includes intraparenchymal, subarachnoid and intraventricular haemorrhage.² Recently described is a case of a 12-year-old girl with SCA, presenting with catastrophic intracranial

haemorrhage; her most recent TCD 6 months prior to presentation was normal.¹⁵ These case reports underline the necessity for detailed screening tests to stratify risk profiles for all kinds of haemorrhagic stroke and emphasise the importance of autopsy investigations, as in the present case.

Learning points

- This is the first histopathology description of cerebral vasculopathy occurring in association with haemorrhage stroke in sickle cell anaemia (SCA).
- This case highlights the unexpected nature and poor outcome associated with a haemorrhagic stroke in children with SCA; and the absence of a preventive strategy.
- There is a need for more up-to-date study of blood pressure and stratification of risk factors for adverse outcome in SCA.

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Competing interests None.

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