CASE REPORT

Moyamoya syndrome in sickle cell anaemia: a cause of recurrent stroke

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SUMMARY

We report a case with interesting imaging findings as well as an unfortunate but not unexpected clinical outcome. Our patient, an 8-year-old Jamaican boy of Afro-Caribbean descent with homozygous sickle cell disease, presented with left-sided upper limb weakness. He had a history of recurrent cerebrovascular accidents and transient ischaemic attacks beginning at 4 years of age. MRI revealed old bilateral infarctions and the ivy sign on fluid-attenuated inversion recovery sequences. MR angiography demonstrated numerous collaterals, most apparently arising from the left internal carotid, consistent with moyamoya syndrome. The patient had a full recovery and remained well for almost 2 years when he suffered another stroke.

BACKGROUND

Sickle cell disease (SCD) is the most common genetic disorder in Jamaica. At our local sickle cell facility, the Sickle Cell Unit (SCU), an average of 1500 children under the age of 18 years of age are seen annually. Based on data generated by this unit, various aspects of the impact of the disease in our community have been elucidated. Seizures and clinical strokes are the most common neurological complications of SCD seen in our population. Cerebrovascular accidents, especially when associated with permanent neurological deficits, are one of the most devastating potential outcomes of SCD as the victims are predominantly children. Moyamoya syndrome is associated with SCD and has implications for patient management as well as outcome. This case will highlight the utility of MRI and MR angiography (MRA) in the diagnosis of this entity. The prevalence of moyamoya in our setting is not known and our discussion will explore the rationale of screening for moyamoya in children with SCD as well as the potential of MRI and MRA as screening tools. To the best of our knowledge, this is the first case of moyamoya in SCD to be reported from our institution.

CASE PRESENTATION

Our patient, a Jamaican male of West African descent, was delivered at 36 weeks gestation by emergency Caesarean section due to maternal pre-eclampsia, weighing 2.8 kg at birth. His only neonatal problem was mild jaundice for a few days. Cord blood analysis revealed the presence of homozygous SCD or sickle cell anaemia (SCA).

At 10 months of age, recurrent acute splenic sequestration led to splenectomy. Dactylitis at 2 years and 10 months, complicated by abscess

formation, required surgical intervention. His developmental history was unremarkable prior to the first stroke. Chronic nasal allergies, eczema, recurrent tonsillitis and upper airway obstruction were treated with nasal steroids and antihistamines. A paternal male sibling had a history of seizures but no cerebrovascular incidents. There was no history of febrile seizures or epilepsy in our patient.

At 4 years of age, he presented with left-sided weakness and drowsiness. Examination revealed a mild left hemiparesis. His haemoglobin (Hb) concentration at the time was 6.5 g/dL. On admission to hospital, CT demonstrated a bland infarct in the right frontal lobe. An exchange transfusion was done and he was referred for physiotherapy as an outpatient. His hemiparesis began to resolve within weeks. In the absence of a chronic transfusion programme, treatment with hydroxyurea (HU) was commenced in an attempt to prevent stroke recurrence.

Eleven months after the first stroke, he presented with his right foot 'not working properly'. On admission to hospital he received an exchange transfusion, but due to technical difficulties no confirmatory neuroimaging was done. His symptoms resolved within 3 days.

At 8 years and 7 months of age, he presented with left-sided weakness, seemingly confined to the upper limb. On examination, his left upper limb was found to be areflexic and grade 3 power was demonstrated at examination. Within an hour of his initial examination, his hand grip improved noticeably. A decision was taken to do MRI and MRA. Of note, this patient was never found to have been hypertensive and his steady state Hb was 8.5 g/dL.

INVESTIGATIONS

CT repeatedly demonstrated infarctions, initially on the right and subsequently bilaterally. There was never any evidence of haemorrhage.

MRI revealed bilateral frontal lobe infarcts (figure 1A, B). There were associated cystic changes and volume loss in the affected lobes consistent with chronic infarction. Flow voids were noted in the basal ganglia, consistent with prominent lenticulostriate arteries and collaterals arising from these vessels, the changes being more marked on the left (figure 2A, B). The ivy sign was evident on the T2-fluid attenuated inversion recovery (FLAIR) sequences, indicative of leptomeningeal collateral flow (figure 1B). Diffusion-weighted images demonstrated no evidence of acute ischaemia, in keeping with a 2 month hiatus postinsult (imaging being delayed due to social reasons).

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Figure 1 (A) Axial fluid attenuated inversion recovery image demonstrating bilateral frontal lobe infarctions with associated cystic changes and volume loss. (B) Again, bilateral infarctions are noted, but in addition the ivy sign is noted in both parietal lobes, being more pronounced on the right (arrow).

MRA demonstrated a narrowing and possible partial occlusion of both middle cerebral arteries, the findings being more marked on the left (figure 3A, B). The branches of these arteries also appeared deficient. The distal internal carotid on the left also appeared deficient. Prominence of the lenticulostriate arteries as well as the presence of collaterals was confirmed. Source images were also helpful in this regard (figure 4).

Transcranial Doppler (TCD), a newly available diagnostic tool at the SCU, was done 1 month after the MRI and MRA. TCD was chosen as it is non-invasive, readily available and at the time presented no additional cost to the patient. It demonstrated decreased flow in both middle cerebral arteries. Of note, no flow was recordable in the distal left middle cerebral artery. Reduced flow rates were demonstrated at the bifurcation of both the right and left internal carotid arteries, however the flow rate on the left appeared more satisfactory. The posterior circulation was unremarkable.

TREATMENT

This patient received standard childhood immunisations: Bacillus Calmette-Guérin vaccine, combined diphtheria, pertussis, and tetanus vaccine, Haemophilus influenzae type B vaccine, polio and hepatitis B with no adverse reactions. He also received

the 23-valent pneumococcal conjugated vaccine at age 4 years. Monthly prophylactic penicillin injections were started at 4 months of age and changed to oral Phenoxymethyl penicillin at 1 year and 10 months of age.

HU was introduced after the first clinical stroke at age 4 years. He was started at 15 mg/kg/day, and the dosage was increased to an maximum tolerated dose of 31 mg/kg/day. The only documented interruption was less than 4 weeks, after his episode at age 8 years.

He is currently maintained on HU 1050 mg (30 mg/kg), amoxicillin 250 mg twice daily, folic acid 5 mg daily and aspirin 81 mg daily orally.

OUTCOME AND FOLLOW-UP

The patient is now 11 years old and, other than concerns with inattentiveness at school, had been well with no neurological episodes since the one at 8 years of age. Unfortunately, he suffered a stroke a few weeks ago. In the light of this most recent event, neurosurgical intervention is being considered.

DISCUSSION

SCD is an inherited genetic disorder resulting from the presence of defective haemoglobin, sickle haemoglobin, in affected

Figure 2 (A) Axial fluid attenuated inversion recovery image demonstrating flow voids in the left parahippocampal gyrus (arrow). (B) Flow voids in the left lentiform nucleus (arrow).

Figure 3 (A) Three-dimensional time of flight image demonstrating an absent left middle cerebral artery, narrowing of the right middle cerebral artery, M1 segment and collateral vessels bilaterally (arrow). (B) Left anterior oblique projection demonstrating the puff of smoke appearance (arrow).

individuals. The disease may be heterozygous such as in HbSC (heterozygous sickle cell disease characterised by the presence of HbS and HbC) or homozygous as in homozygous sickle cell disease. SCA refers to the presence of homozygous disease (Serjeant and Serjeant).¹ Jamaica is the only territory in the English-speaking Caribbean countries with a comprehensive sickle cell facility, the SCU. The SCU clinic attends to an average of 1500 children under the age of 18 years annually. Homozygous SCD has been found to occur in 1:300 live-births per year.² The phenotypic expression of this disorder has exceeded the early hypotheses with regard to the pathogenesis of complications of this disorder. The tendency for the formation of sickled red blood cells under conditions of decreased oxygen tension explains only some of the complications.

The phenomenon subsequently referred to as moyamoya disease was first described in 1955 by Takeuchi and Shimizu.³

The name is descriptive of the angiographic appearance of the collateral vessels, being reminiscent of a puff of cigarette smoke, and was coined by Suzuki and Takaku.⁴ The disease is of unknown aetiology, the collateral vessels apparently being a response to a decrease in the calibre of the larger cerebral vessels including the circle of Willis. This was demonstrated to be the result of a progressive fibrolamellar thickening of the tunica intima and overgrowth of the vascular smooth muscle cells.⁵ There are numerous hypotheses in the literature as to the pathogenesis of moyamoya disease. Vascular endothelial growth factor (VEGF) is a glycoprotein known to be involved with neo-vascularity in tumours⁶ and ischaemic changes in the brain.⁷ Sakamoto *et al*⁷ demonstrated an increase in VEGF in patients with moyamoya disease. Basic fibroblast growth factor has also been shown to be increased in the CSF of patients with moyamoya disease.⁸ Yamauchi *et al*⁹ described an increased familial occurrence of the disease in 1997 and Kamada *et al*¹⁰ more recently identified a gene as being involved in the development of the disease.

The moyamoya phenomenon can also be demonstrated in other conditions such as SCD, systemic lupus erythematosus,¹¹ neurofibromatosis type 1,¹² previous radiation therapy, tuberous sclerosis, periarteritis nodosa,¹³ mesial temporal sclerosis,¹⁴ thyrotoxicosis¹⁵ and Down's syndrome.¹⁶ When there is known underlying pathology, the condition is correctly referred to as moyamoya syndrome.^{4 17}

Children with SCA are at significantly increased risk of cerebrovascular accidents. This was first described in 1923 by Sydenstricker, who reported convulsions and haemiplegia in a 5-year-old boy, and left hemiparesis in a 3-year-old baby.¹⁸ It was thought that these events were secondary to small vessel disease and vaso-occlusion secondary to the presence of sickled cells.^{19 20} However, in 1972, Stockman *et al*²¹ demonstrated the presence of large vessel occlusion at cerebral angiography in 6 of 7 patients with SCA and neurological deficits. The internal carotid artery was involved in all cases. The anterior cerebral and middle cerebral arteries were also involved in some cases.

Yamada *et al*²² demonstrated the utility of three-dimensional time of flight in diagnosing the presence of moyamoya disease. When compared with catheter angiography, MRA was still found to be robust,²³ and when combined with MRI the sensitivity and specificity were found to be 92% and 100%, respectively. MRA has subsequently become a first-line diagnostic tool for diagnosis of moyamoya, being non-invasive without the use of intravenous contrast agents to which persons with SCD are more susceptible.

Figure 4 Source image demonstrating collaterals.

The presence of moyamoya is an important finding in patients with SCD potentially affecting the management as well as the prognosis and has been found to be a predictor of recurrent stroke.²⁴

Seizures and stroke were found to be the most common neurological events in SCD in a Jamaican cohort. Balkaran *et al*²⁵ found an incidence of 7.8% by age 14 years in patients with homozygous disease. Ali *et al*²⁶ found the prevalence of seizure activity in the cohort to be 7%, and seizure activity defined as epilepsy to be 2.2%, 4–5 times higher than in the general Jamaican population. Telfer *et al*²⁷ found a risk of 4.3% for overt stroke in a neonatal cohort in East London, a population with a large percentage of Afro-Caribbean persons.

Children with SCD tend to suffer ischaemic infarctions, as did our patient.²⁸ SCD is a risk factor for arterial ischaemic stroke.²⁹ Ischaemic strokes were also found to be more common in the Jamaican cohort.³⁰ Our patient was maintained on HU and aspirin since the first episode. Aspirin is useful because it is an antiplatelet agent. Stenotic blood vessels facilitate the formation of thrombi with the potential for microemboli. The anti-inflammatory properties of aspirin might also be beneficial.^{31 32} HU has several potential beneficial effects in stroke prevention. These include increased production of foetal Hb, reduced marrow production of neutrophils and reticulocytes, an increase in the mean corpuscular volume and production of nitric oxide, with the result of reduction in sickled cells, reduction of haemolysis and improved blood flow.^{33–37}

Imaging findings in our patient were very interesting. MRI revealed old infarctions and evidence of enlargement of the lenticulostriate arteries, with collaterals demonstrable as flow voids in the basal ganglia. MRA demonstrated stenosis of distal internal carotid arteries as well as marked attenuation of the left middle cerebral artery, the right middle cerebral artery being less affected. Basal collaterals were demonstrated. The MRA findings were consistent with grade III disease based on the Suzuki grading system.⁴ The ivy sign was also seen on FLAIR images.

The ivy sign was first described by Ohta *et al*³⁸ as dramatic leptomeningeal enhancement postadministration of intravenous contrast, reminiscent of creeping ivy, attributed to the presence of leptomeningeal neovascularity. While the ivy sign is better demonstrated on gadolinium-enhanced T1-weighted images,³⁹ it can be demonstrated on FLAIR images.⁴⁰ This finding has been found to be representative of decreased cerebral perfusion.⁴¹ Kawashima *et al*⁴² demonstrated a decrease in the presence of the ivy sign postrevascularisation procedures. Lee *et al*⁴³ further suggested the ivy sign as a potential substitute for other modalities postrevascularisation, being better tolerated by patients.

Catheter angiography was not done in our patient and is not recommended for the diagnosis of moyamoya, but is advisable when neurosurgical intervention is being considered.²³ Some of the limitations of MRI combined with MRA include overestimation of areas of stenosis and failure to adequately demonstrate extracranial vessels.^{23 44} Preoperatively, four vessel angiography and external carotid angiography are routine. Patients might also be required to undergo EEG, perfusion imaging (whether CT or MR), positron emission tomography and single-photon emission CT as these studies can be used to further define areas of decreased cerebral perfusion.⁴⁴ There are direct and indirect methods of surgical revascularisation, indirect methods being favoured in the paediatric population due to the smaller vessel size. One direct method is anastomosis of the superficial temporal artery to the middle cerebral artery.⁴⁴ Pial

syngangiosis is an indirect method involving suturing a donor artery directly to the pial surface. The superficial temporal artery is commonly used and access to the pia is gained via craniotomy subjacent to the in situ donor artery.⁴⁵

TCD findings were consistent with MRA findings with respect to the narrowed major cerebral arteries. However, it would not have been possible to make the diagnosis of moyamoya at TCD as the collateral vessels are too diminutive and tortuous to insulate reliably.

The case of this unfortunate child serves as a reminder of the potentially devastating neurological consequences of SCA. He suffered recurrent strokes despite maintenance on HU. Chronic blood transfusion is recommended for stroke prevention in high-risk patients with SCD (patients with cerebral blood flow in excess of 200 cm/s).^{46 47} Maintenance on HU is not standard practice; however, owing to a severe shortage of blood in our setting, chronic transfusion for stroke prevention is not a viable option. While the evidence with respect to HU in stroke prevention is limited, Ware *et al*⁴⁸ found a lower than expected rate (19% actual stroke rate as opposed to an expected 50%) of stroke recurrence in 16 patients in whom transfusions were discontinued and switched to HU. The findings by Lefevre *et al*⁴⁹ were also supportive. At our institution, HU has also been shown to be associated with a reduction in the recurrence of stroke in children with SCD.³⁰ So without the possibility of chronic transfusions, HU was employed.

Dobson *et al*²⁴ reported the moyamoya phenomenon in a child preceding the occurrence of stroke by 3 months. This child had been found to have an abnormal TCD in the STOP trial.⁴⁶ In our setting, screening for moyamoya is not done. Indeed, there are no protocols established worldwide for screening for this entity. Therefore, it stands to reason that the prevalence of moyamoya in populations of sickle cell patients is not known. It is therefore possible that a significant proportion of patients have moyamoya at the time of their first stroke.

This patient was discovered to have moyamoya, which is likely to have contributed to his clinical outcome. The progression of moyamoya is variable, but surgical intervention, especially prior to the onset of neurological deficit, can improve the prognosis.¹⁷ Guzman *et al*,⁵⁰ in a cohort of 329 patients, found a cumulative risk of 5.6% of stroke or haemorrhage after revascularisation surgery compared with as much as 65% in untreated symptomatic patients. They recommend surgical intervention.⁵⁰ The case also serves to remind us of the diagnostic utility of MRI and MRA as well as the potential importance of determining the prevalence of moyamoya.

Learning points

- ▶ Moyamoya disease can only be diagnosed in a patient with no underlying cause for arterial disease. Similar findings in patients with underlying causes are correctly referred to as moyamoya syndrome.
- ▶ Detecting moyamoya syndrome is important in patients with sickle cell disease (SCD) as it may affect both management strategies as well as the prognosis.
- ▶ This case demonstrates the utility of MRI and MR angiography (MRA) in the diagnosis of the moyamoya phenomenon.
- ▶ Moyamoya has been shown to predate clinical stroke therefore screening high risk patients might be justified.

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