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Clinical Study

Sickle cell disease and posterior reversible leukoencephalopathy

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ABSTRACT

Sickle cell disease can present with neurological manifestations. One such presentation is with posterior reversible leukoencephalopathy also known as reversible posterior leukoencephalopathy. The condition is classically described as reversible over time; it commonly presents with oedematous changes involving the white matter of the occipital and parietal regions. Only a few patients with the association between sickle cell disease and posterior reversible leukoencephalopathy have been described in the adult literature. We present two patients from our institutions to emphasise the association between the two conditions and summarise the published cases in the literature.

1. Introduction

Patients with sickle cell disease can have significant brain involvement as part of their disease process. It has been reported that up to 11% of young patients under the age of 20 had definite strokes, whilst up to 30% would have evidence of silent cerebral infarctions [1–3].

Posterior reversible leukoencephalopathy (PRES), also known as reversible posterior leukoencephalopathy, is a condition characterised by seizures, headaches, encephalopathy, visual symptoms and focal neurological deficits [4]. Neuroimaging, especially MRI, reveals oedematous changes commonly in the white matter of the occipital and parietal regions, but can also involve the frontal lobes, inferior temporal-occipital junction and the cerebellum [5,6]. The condition is classically described as reversible with resolution of the white matter changes over time [7].

There have been a few patients with sickle cell disease and PRES described [8–14]. The majority of the patients are in the paediatric population and associated with hypertension. In some of these patients there have been recurrent episodes of PRES [8,12,14]. We present two patients from our institutions to highlight the association between the two conditions.

2. Patient 1

A 30-year-old woman of Middle Eastern origin presented to a district hospital with a 3 week history of progressive confusion, lethargy and discoloured sputum. This was complicated by vomiting for the previous 3 days and associated reduced oral intake. Her significant medical comorbidities included sickle cell thalassemia complicated by osteoporosis, bilateral hip replacement, splenectomy, gastrectomy for gastric outlet obstruction, prior deep venous thrombosis and pulmonary embolism and a subdural bleed after warfarinisation. Her medications included methadone 30 mg three times a day, gabapentin 300 mg four times a day (recently withheld for drowsiness), rabeprazole 20 mg daily and hydroxyurea 200 mg daily. She was a non-smoker and did not drink alcohol.

She was drowsy on examination, saturating 95% on 2 L of oxygen via nasal prongs with clinical and radiological evidence of an infective respiratory process. She was anaemic (haemoglobin 54 g/L, normal 115–165 g/L) with haemoglobin S of 40.2% (normal = 0), and had a neutrophilic leukocytosis (white cell count 15.1 $\times$ 10^9/L, normal 3.7–9.5 $\times$ 10^9/L). She was hypernatraemic

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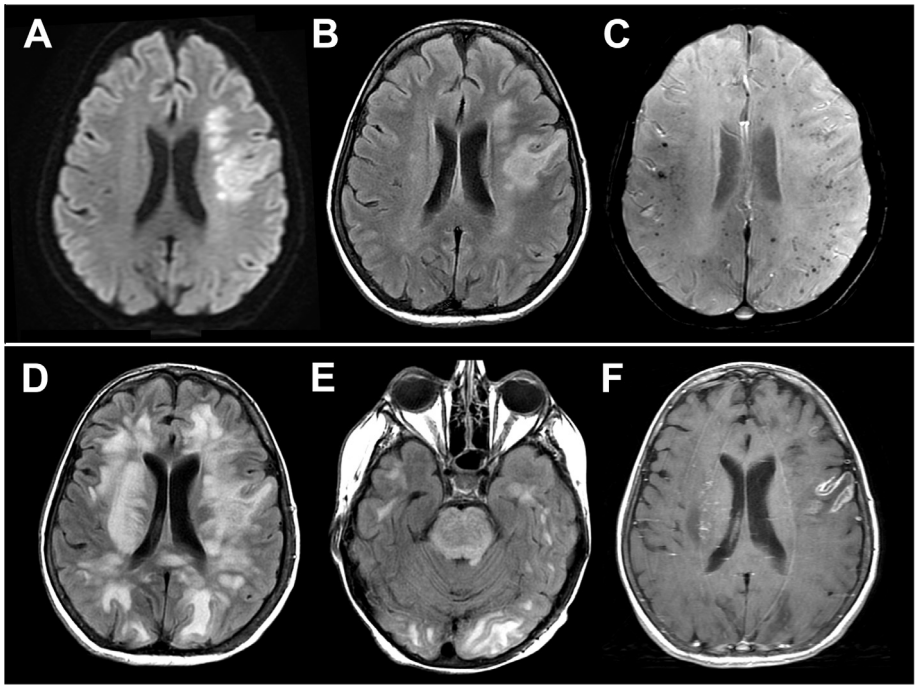

Fig. 1. Axial diffusion weighted (A) and fluid attenuated inversion recovery (FLAIR) (B) MRI 11 days after presentation showing acute/subacute left frontal infarction. Axial susceptibility weighted imaging (C) showed innumerable hypointense foci, likely microhaemorrhages, throughout both cerebral hemispheres. Progress axial FLAIR MRI performed 6 days later showing extensive confluent altered signal intensity in the white matter of both cerebral hemispheres (D), the cerebellum (not shown) and the brainstem (E). Gadolinium-enhanced axial T1-weighted MRI showing scant or minimal enhancement in the white matter, and (F) gyriform enhancement of the subacute left frontal infarction.

(153 mmol/L, normal 135–145 mmol/L) and hypokalaemic (2.6 mmol/L, normal 3.2–5.0 mmol/L). She was transfused four units of red blood cells and transferred to our institution with worsening progressive respiratory failure. Upon review at our facility she was hypoxic on non-invasive ventilation, fluid overloaded and was treated for a sickle cell crisis. After plasma exchange with five units of packed cells her haemoglobin S reduced to 11.6%, and subsequently she experienced fluid overload and required dialysis.

A neurology consult was obtained on day 11 post-admission in the intensive care unit because the patient was persistently drowsy after cessation of sedation and not obeying commands. Examination with the patient intubated showed no cranial nerve changes but revealed a probable receptive aphasia, weakness of the right hand with some pyramidal manifestations (hyperreflexia, clonus and upgoing plantar reflex).

Initial MRI examination showed an acute/subacute left middle cerebral artery infarction and innumerable foci of susceptibility, presumed to be microhaemorrhages, throughout both hemispheres and the posterior fossa (Fig. 1A–C). Magnetic resonance angiography of the circle of Willis was normal (not shown). Cerebral catheter angiography did not show any intracranial/extracranial cerebral vessel irregularities. She was started on aspirin for management of her stroke. MRI examination 6 days later revealed extensive symmetrical altered signal intensity in the white matter of both hemispheres, brainstem and cerebellum suggestive of PRES, despite a normal blood pressure (systolic ranging from 90–120 mmHg) (Fig. 1D–F). The remainder of her inpatient stay was complicated by seizures and ongoing sepsis (respiratory source). Transoesophageal echocardiogram did not demonstrate thrombus or patent foramen ovale. Cerebrospinal fluid (CSF) analysis showed two red blood cells/uL with no white cells, CSF glucose was 4.0 mmol/L (normal 2.2–3.9 mmol/L) and protein 1.09 g/L (normal 0.15–0.45 g/L). Despite intensive medical treatment the patient died of sepsis on day 33.

3. Patient 2

A 17-year-old African girl with homozygous sickle cell disease and frequent painful crises was admitted to hospital for a reduced intensity (non-myeloablative) conditioning, human leukocyte antigen-matched sibling donor bone marrow transplant. She was treated with the appropriate supportive care according to the Paediatric Blood and Marrow Transplant Consortium's Protocol for reduced intensity conditioning in sickle cell disease. She received cyclosporin (aiming for a trough level of 200 mg/L), short course methotrexate and prednisone for graft *versus* host disease prophylaxis.

On the day of the transplant she received a moderate cell dose of 1.8 total nucleated cells $\times 10^8$/kg with no complications. She had polymerase chain reaction evidence of adenovirus early post-transplant and this was treated with cidofovir. There was no acute graft *versus* host disease in the first 30 days post-transplantation, nor veno-occlusive disease and the marrow engrafted rapidly with neutrophil count >1.5 $\times 10^9$/L by day 12. She was independent of platelet transfusion by day 10. A gram negative urinary tract infection was treated with oral augmentin. However, by day 16 post-transplant she had developed systemic hypertension and persistent headaches and nifedipine was added to her regimen. Methicillin-resistant *Staphylococcus aureus* positive skin lesions were treated topically and with ciprofloxacin and she was discharged on day 29 with controlled blood pressure, stable renal function and healing skin lesions. As an outpatient, she developed diarrhoea and some mild pulmonary erythema deemed to constitute mild acute graft *versus* host disease.

One week later she presented with acute visual loss, worsening headache and vomiting. CT scans showed bilateral occipital infarctions consistent with the posterior reversible encephalopathy syndrome. At this time she had <1% haemoglobin S and neither the clinical picture nor CT scan were consistent with an acute stroke.

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