Cerebral fat embolism syndrome (CFES) is a neurologic syndrome occurring in up to 60% of patients with fat embolism syndrome (FES). The defining features of FES include respiratory, neurologic and dermatologic features. The classical explanation is release of fat emboli into the circulation after long bone fractures, but the clinical syndrome of FES only occurs in 0.5-3% of cases, typically within 12-72 hours. The pathophysiologic mechanism appears to involve a combination of mechanical occlusion by fat emboli in the microvasculature, and biochemical toxicity of free fatty acids locally released from embolic material. Neurologic presentation may include confusion, seizure, focal neurologic deficits or coma. Magnetic resonance imaging (MRI) is the diagnostic test of choice, usually demonstrating multifocal punctate lesions preferentially involving the cerebral white matter. These are hyperintense on T2-weighted images, and demonstrate enhancement on gadolinium-enhanced T1 sequences. Diffusion weighted imaging (DWI) is the recommended MRI sequence for early diagnosis. Most patients have a full neurologic recovery, although there are currently no clinical or imaging criteria which can predict outcome. We report two cases of CFES with numerous restricted diffusion lesions on DWI, in which neurologic outcome was poor.

Case 1: A healthy 20-year-old woman fractured her left femur during a cycling collision. She had no other injuries and was neurologically intact. Twenty-four hours later, the patient had fracture fixation with intramedullary nailing. After extubation, she was confused, febrile and short of breath, although no rash was present. Over several hours she developed worsening dyspnoea, tachypnoea with increasing oxygen requirements (lowest pO2 66 with pH 7.31, pCO2 45). She was diagnosed with acute respiratory distress syndrome on the basis of diffuse alveolar opacification on chest x-ray, and was re-intubated. This patient required intravenous fluids and norepinephrine to...

Figure 1: (A) T2-weighted axial image at the level of the lateral ventricles demonstrates innumerable hyperintense foci of abnormal signal intensity within the cerebral hemispheric white matter bilaterally, including the corpus callosum, and associated with mild generalized cerebral swelling; (B,C) DWI and ADC imaging demonstrating diffuse and marked restricted diffusion in the same regions of T2 signal abnormality seen in image ‘A.’
maintain systolic blood pressure above 90 mmHg for 24 hours. There were no periods of hypotension while on continuous monitoring in ICU. Work-up for alternative aetiologies including blood/urine/sputum cultures and blood work were consistent with systemic inflammatory response, with platelet count dropping to 104 x10^9/L, and no infection identified.

Three days later, her respiratory picture improved but she remained unresponsive. Brain CT scan showed subtle diffuse white matter abnormalities. Magnetic resonance imaging demonstrated marked diffuse white matter increased signal on T2 and fluid attenuated inversion recovery (FLAIR) imaging, restricted on DWI (Figure 1).

Three months post-injury, the patient was awake and could fix objects. However, she was aphasic and unable to follow commands. She had spasticity, hyperreflexia and clonus in all limbs but could localize pain. There was no evidence of higher cortical function.

**Case 2:** A healthy 21-year-old male suffered a right leg injury and brief loss of consciousness from a motor vehicle collision. The patient recovered consciousness after two minutes, and GCS was 15 at presentation. Computed tomogram scan of the brain was normal, and x-rays of his right femur revealed a mid-shaft transverse fracture. Eight hours later, the patient developed confusion and mild hypoxia which was responsive to oxygen. The patient had open reduction and internal fixation of the fracture. Intraoperatively, he became further hypoxic (PaO2 nadir of 73, with pH 7.47, pCO2 30) and hypotensive, and this was rapidly corrected with high-flow oxygen and vasopressor support. He remained intubated post-operatively but no longer required vasopressors, and there were no further periods of hypotension. Chest x-ray showed bilateral diffuse lung infiltrates. No rash was present although platelet count dropped to 83 x10^9/L. Blood work, urine analysis and cultures of blood/urine/sputum did not reveal an alternative diagnosis to FES.

Nine days later, his neurologic status had not improved despite resolution of respiratory failure. He remained unresponsive, but had intact brainstem reflexes, with extensor posturing to pain, and hyperreflexia and clonus. The MRI showed numerous T2 high signal white matter lesions that were restricted on DWI. Follow-up MRI three months post-admission showed persistence of T2 high signal lesions and marked cerebral volume loss (Figure 2). Repeated EEG records demonstrated diffuse encephalopathy with no epileptiform abnormality. Transthoracic echocardiogram was normal. A transesophageal echocardiogram was not performed. Only marginal neurologic improvement occurred and after eight months, he remained in a minimally responsive state, with diffuse spasticity, and requiring tube feeding.

**Discussion**

Ongoing research in CFES has not yet revealed a prognostic marker. Takahashi and others demonstrated that T2 lesion load correlated with initial severity of CFES; however, this was not predictive of final neurological outcome. Patients with poor outcome who developed brain atrophy and multiple infarctions on follow-up imaging had a high lesion burden but this could not be distinguished from other patients with similar neuroimaging who made full recovery. In a report of a patient with CFES and enduring neurological deficits, it was suggested that the presence of numerous restricted DWI lesions was associated with poor outcome. Another series reported five CFES patients with restricted diffusion on MRI with no predictable effect on
prognosis, although the restricted diffusion lesion burden was low in their representative case images. Marshall reported two patients with lesions demonstrating restricted diffusion, the first having a low lesion burden and complete recovery, and the second patient having a much higher lesion burden with persistent neurological deficits. Our series contributes by adding two patients with large burdens of restricted diffusion lesions that ultimately had poor prognosis. Significant cerebral volume loss was demonstrated on follow-up imaging. In consideration of our cases and other reported patients with restricted DWI lesions, we suggest that the quantity of restricted DWI lesions correlates with irreversible brain injury, subsequent cerebral volume loss, and long-term clinical outcome.

In animal models of CFES, lesions showing ADC isointensity and gadolinium enhancement are reversible, suggesting a subset of lesions with blood-brain barrier disruption without infarction. These lesions are associated with minimal or no histologic changes in similar models. To this effect, case reports demonstrating reversible non-restricted DWI lesions and subsequent neuroradiologic and clinical resolution have been reported. Patients with initially severe phenotype who recover completely may have a predominance of these reversible lesions.

The above hypothesis may have utility in the management of CFES. The presence of a patent foramen ovale (PFO) has been correlated with entry of a higher embolic load into the cerebral vasculature. It has been suggested that high embolic load on transesophageal echocardiography (TEE) can identify high-risk patients. Forteza and others reported a patient with large volume post-traumatic fat emboli on intracranial doppler, with DWI changes on brain MRI, who had a large PFO. The patient had urgent percutaneous PFO closure prior to surgical manipulation of her fracture, with reduction in fat emboli seen on Doppler ultrasound. A higher fat embolism burden has been shown to increase the incidence of CFES, although CFES also occurs in the absence of intracardiac shunts. Nonetheless, reports exist of more severe phenotype associated with right to left shunts. Burden of restricted DWI lesions could be used as an objective, noninvasive test to identify patients with higher probability of poor outcome, and permit further investigation with TEE to visualize right to left shunts. Corrective procedures could potentially be implemented to reduce the embolic burden. An association between severe MRI changes and large right to left shunts may exist and should be further explored.

We suggest that DWI may have prognostic value in differentiating outcome in CFES. Full neurological recovery is typical for most cases of CFES, although the presence of numerous restricted diffusion lesions on DWI should alert clinicians to the possibility of a poorer clinical outcome, and help guide discussions regarding prognosis and potential for longterm disability with families. Further study should attempt to validate these preliminary observations, and ideally find use to guide interventions to avoid neurological sequelae.

REFERENCES