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LETTER TO THE EDITOR

Delayed cerebral microbleeds in a patient with cerebral fat embolism

Yaoyao Shen[1] · Yanqin Guan[1] · Jingyan Chai[1] · Tingmin Dai[1] · Yijun Suo[1]

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Dear Editor,

Fat embolism syndrome, frequently associated with displaced long bone fracture of the lower extremities, is characterized by respiratory disability, petechial skin rash, and neurological symptoms. It is estimated that the incidence of cerebral fat embolism (CFE) is 0.9–2.2% [1]. The clinical presentations of CFE can vary greatly, ranging from mild confusion to coma, and rarely include seizures and focal findings. Five distinctive magnetic resonance imaging (MRI) patterns of CFE, including scattered cytotoxic edema, confluent cytotoxic edema, vasogenic edema, petechial hemorrhage, and chronic sequelae, have been summarized by Kuo et al. after systematic review of the literature [2]. Previous case reports have suggested that it is common to detect diffuse microbleeds on susceptibility-weighted imaging (SWI). However, the exact time and mechanism of cerebral microbleeds (CMBs) are not well understood. Here, we describe a CFE patient presented with delayed CMBs after artificial bone replacement operation for femoral neck fracture.

A 80-year-old woman was slipped and complained of left hip pain. X-ray disclosed left femoral neck fracture (Fig. 1). She was conscious on admission. The next day, she underwent an artificial femoral head bone replacement operation. Twenty-four hours after the operation, she experienced lost consciousness with a Glasgow Coma Scale of 6 (E1V1M4). Her vital signs were a temperature of 36.5 °C, a heart rate of 90 beats per minute, blood pressure of 168/72 mmHg, and O2 saturation 95%. Neurological examination did not reveal focal deficits. Laboratory data and chest computed tomography (CT) showed unremarkable findings. Subsequently, brain MRI illustrated small, patchy, or confluent hyperintense scattered throughout bilateral cerebral and cerebellar hemispheres on T2-weighted and fluid-attenuated inversion recovery (FLAIR) images with restricted diffusion (Fig. 2a–d). SWI showed no abnormalities (Fig. 2e). Moreover, magnetic resonance angiography (MRA) revealed no vascular abnormalities. Six days later, repeated diffusion-weighted images (DWI) demonstrated the hyperintense foci resolved (Fig. 2f). However, the SWI scanning demonstrated uncountable spotty lesions in the white matter, corpus callosum, and cerebellum (Fig. 2g, h). Contrast-enhanced transcranial Doppler (c-TCD) revealed no evidence of intracardiac shunt. Based on the clinical presentation and MRI findings, the diagnosis of CFE can be established. As the patient's mental status improved slightly during hospitalization, she was discharged on day 12 after admission.

Discussion

Fat embolism syndrome, as a rare complication of the pelvis or long bone fractures, was first documented in Zenker in 1862 [3]. A wide spectrum of clinical manifestations of CFE have been described in the literature, including headache, different levels of disturbance of consciousness, focal neurological deficits, seizures, irritability, and delirium. Two mechanisms may explain how fat globules can enter the arterial circulation. First, fat globules can directly enter the left atrium from the right heart via the presence of right-to-left shunts (RLS). Second, fat vacuoles smaller than 5 μm could directly pass through the lung capillaries to reach the arterial system, resulting in arterial embolism without significant pulmonary injury [4].

Histologically, previous autopsy studies of CFE demonstrated multiple petechiae in the brain. However, conventional MR techniques can hardly detect hemorrhagic lesions. SWI, a newer MRI technique, is extremely useful for detecting microbleeds owing to its high sensitivity for detecting blood products. In CFE, CMBs can be noted in all stage, ranging from within the first day after fracture to the whole course of the disease. Microbleeds, predominantly occurred in the

✉ Yaoyao Shen
15270881796@163.com

[1] Department of Neurology, The Affiliated Hospital of Jiujiang University, No.57 Xunyang East Rode, Xunyang District, Jiujiang 332000, Jiangxi Province, People's Republic of China

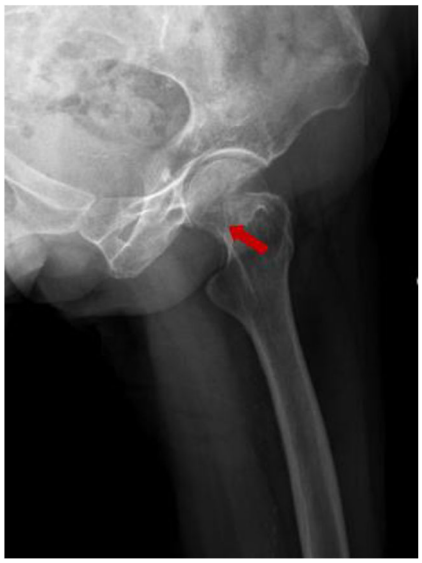

Fig. 1 On admission, X-ray showed left femoral neck fracture (red arrow)

cerebral and cerebellar white matter and the corpus callosum, is thought to represent small hemorrhagic embolic infarctions, with occlusive fat embolus resulting in intravascular increased pressure and vessel wall rupture.

In our patient, lacking of clinical presentation of respiratory failure and CMBs on initial SWI scaning, there is a challenge in the diagnosis of CFE. Whereas the history of femoral neck fracture as well as the delayed CMBs further support the diagnosis. To date, c-TCD has been widely used in detecting RLS with high sensitivity. The presence of RLS is related to larger and more frequent microembolic signals to the brain [6]. In this case, however, c-TCD detection failed to provide the evidence of intracardiac shunt and there were no obvious pulmonary symptoms or signs. Hence, the presumable mechanism of CFE in the absence of RLS is that fat emboli are very small and deformable and could directly pass through the pulmonary circulation to reach the arterial system when they are forced into peripheral pulmonary capillaries. Moreover, our case suggests CMBs may be delayed pathophysiological process secondary to fat embolism. However, the mechanism of delayed microbleeds remains unclear. Triolein, the predominant fat in bone marrow and the major constituent of embolized fat in humans, has been used in animal model of CFE. Kim et al. performed a study to evaluate the occurrence of hemorrhage in the cat brain by SWI. Hemorrhage was not obvious until 4 days after infusion of triolein. They suggested fat emboli were fluid and deformable, and can penetrate capillaries. The emboli may pass into veins through a temporary hold-up in systemic capillaries. Hence, the delayed hemorrhage was probably attributed to a delayed penetration of the triolein, which resulted in secondary extravasation of red blood cells into the parenchyma. Moreover, hemorrhage may occur earlier when triolein is significantly embolized due to the increased chances of mechanical disruption of the blood vessel [5].

In conclusion, in patients who suffer from long bone fractures with consciousness disturbance, SWI may help to clarify the etiology of CFE. Further dynamic MRI and animal model studies are needed to investigate the exact time and mechanism of CMBs in CFE patients.

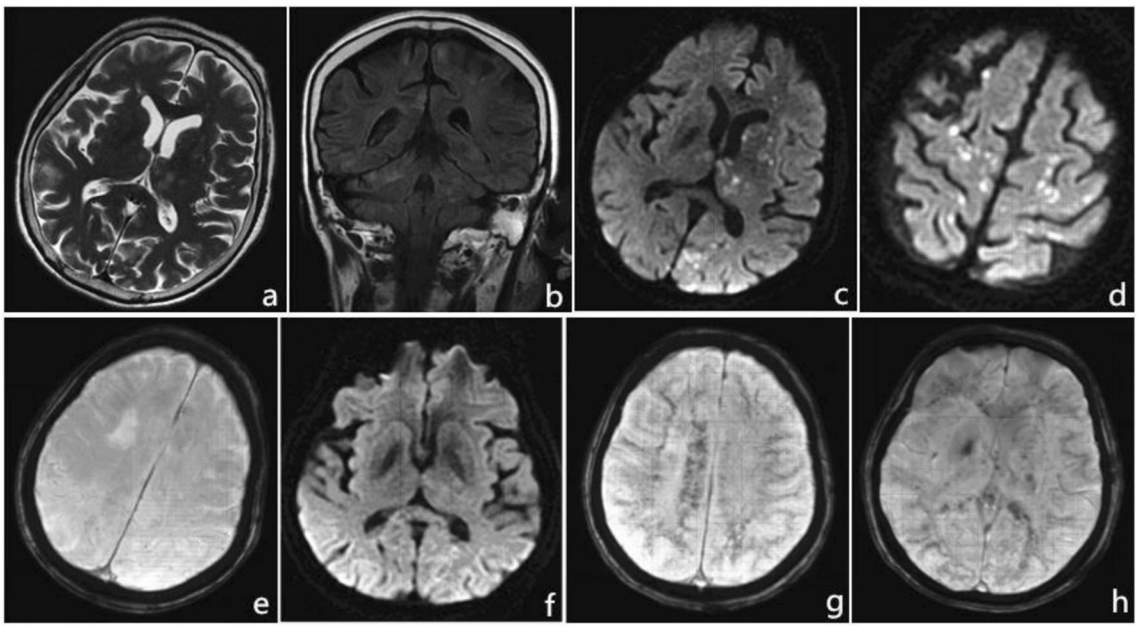

Fig. 2 Brain MRI acquired after the onset of CFE. Axial T2-weighted (**a**) and coronal FLAIR (**b**) images showed multiple dot-like or patchy hyperintense lesions in the bilateral cerebral and cerebellar hemispheres. Axial DWI demonstrated restricted diffusion areas in the same location (**c**, **d**). SWI showed no abnormalities (**e**). 6 days later, the hyperintense foci resolved on DWI (**f**). A repeated SWI scanning illustrated uncountable microbleeds in the white matter, corpus callosum, and cerebellum (**g**, **h**)

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

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