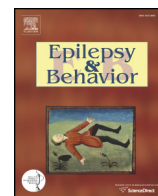




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Brief Communication

Super-refractory nonconvulsive status epilepticus secondary to fat embolism: A clinical, electrophysiological, and pathological study

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ABSTRACT

Background: Fat embolism syndrome (FES) is a rare complication of long-bone fractures and joint reconstruction surgery. To the best of our knowledge, we describe the clinical, electrophysiological, neuroimaging, and neuropathological features of the first case of super-refractory nonconvulsive status epilepticus (sr-NCSE) secondary to fat embolism.

Clinical case: An 82-year-old woman was transferred to our intensive care unit because of a sudden decrease of consciousness level, right hemiparesis, and acute respiratory failure in the early postoperative period of knee prosthesis surgery. Brain computed tomography (TC) including angio-CT and CT perfusion was normal. An urgent video-electroencephalography (v-EEG) evaluation showed continuous sharp-and slow-wave at 2.0–2.5 Hz in keeping with the diagnosis of generalized NCSE. Epileptiform discharges ceased after the administration of 5 mg of intravenous diazepam, and background activity constituted by diffuse theta waves was observed without clinical improvement. Treatment with levetiracetam (1000 mg/day) and sedation with propofol and midazolam were initiated. Moreover, continuous v-EEG monitoring was also started. Despite antiepileptic therapy, epileptiform activity recurred after the interruption of profound sedation, and valproate and lacosamide were added during the ensuing days. Magnetic resonance imaging (MRI) disclosed small scattered foci of acute ischemic infarcts and diffuse petechiae involving the basal ganglia and pons and centrum semiovale in keeping with fat embolism. Super-refractory nonconvulsive status epilepticus remained without control for 2 weeks. Finally, the patient died. The clinical autopsy revealed a bilateral lung fat embolism associated with a hemorrhagic infarction in the left lower lobe. Fatty lesions were also seen in the intestine and pancreas. Scattered microscopic cerebral infarcts associated with fat emboli in the capillaries were noticed, affecting both supra- and infratentorial structures. In addition, occasional focal areas of ischemic injury showing filiform neurons with reactive astrocytic gliosis background consistent with acute lesions were observed in CA3.

Conclusions: Fat embolism should be considered a potential cause of sr-NCSE.

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1. Introduction

Nonconvulsive status epilepticus (NCSE) is a pleomorphic epileptic condition in which behavior disturbance and the level of consciousness may range from minimal to coma [1,2]. Although more commonly

recognized as an etiology of mental status changes in a patient who has suffered trauma with long-bone fractures, fat embolism syndrome (FES) is a rare but potential mechanism of encephalopathy or even coma in patients who previously underwent orthopedic procedures or cardiac surgery. In addition to the central nervous system manifestations, this syndrome is also characterized by pulmonary and cutaneous symptoms.

To the best of our knowledge, we describe the clinical, electrophysiological, neuroimaging, and neuropathological features of the first case of super-refractory nonconvulsive status epilepticus (sr-NCSE) secondary to fat embolism.

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Coma Scale 3). The second head CT scan was normal, and an urgent videoelectroencephalography (v-EEG) evaluation was requested. The v-EEG showed continuous sharp-and slow-wave complexes at 2.0–2.5 Hz in keeping with the diagnosis of generalized NCSE [3]. Epileptiform discharges ceased after the administration of 5 mg of intravenous diazepam, and background activity constituted by diffuse theta waves was observed. However, the mental state of the patient remained unchanged. In view of these findings, the patient was evaluated with continuous scalp v-EEG and bilateral bispectral index (BIS) monitoring. Treatment with levetiracetam (1000 mg/day) and sedation with intravenous propofol (2 mg/kg/h) and midazolam (0.05 mg/kg/h) were initiated. During profound sedation, epileptiform discharges were abolished and a burst-suppression EEG pattern was obtained. Despite antiepileptic therapy, epileptiform activity consisting of generalized periodic discharges (GPDs) at 2.5 Hz recurred after the interruption of profound sedation (Fig. 1), and valproate (1500 mg/24 h) and lacosamide (400 mg/24 h) were added during the ensuing days. At that moment, medical and toxic causes were ruled out as the etiology of NCSE. Given the history of orthopedic surgery, the possibility of massive fat embolism was considered. Fundus examination revealed petechiae and fat particles. On day 14 after admission, cranial magnetic resonance imaging (MRI) disclosed small scattered foci of acute ischemic infarcts and diffuse petechiae involving the basal ganglia and pons and centrum semiovale in keeping with fat emboli (Fig. 2). After

2 weeks under antiepileptic treatment, NCSE was completely controlled and profound sedation stopped. Seven days after interruption of sedation (on day 21 after admission), she did not exhibit spontaneous eye opening nor motor activity following painful stimuli. She could not follow simple commands, and her Glasgow Coma Scale score was 3. Given the advanced age of the patient, the family refused further aggressive intervention. Finally, the patient died, and permission for necropsy was obtained.

2.1. Histologic study

After obtaining full ethical permission following consent by the next of kin, the brain and spinal cord were fixed in 10% formalin for three weeks. Selected areas were embedded in paraffin. Sections were stained with hematoxylin–eosin and Klüver–Barrera staining. The chosen paraffin sections were immunostained with antibodies for neurodegeneration study such as PHF-tau (monoclonal AT8, Thermo Scientific, 1:80), b-amyloide (monoclonal 6F/3D, Dako, 1:20), and GFAP (polyclonal, Dako RTU).

The clinical autopsy revealed a bilateral lung fat embolism associated with a hemorrhagic infarction in the left lower lobe. Fatty lesions were also seen in the intestine and pancreas. Scattered microscopic cerebral infarcts associated with fat emboli in the capillaries were seen, affecting both supra- and infratentorial structures (Figs. 3 and 4). In addition, focal areas of ischemic injury showing filiform neurons with reactive astrocytic gliosis background consistent with acute lesions were seen in CA3 (Fig. 5). Moreover, in CA2, there was a chronic mesial sclerotic focus with gosh tangles related with neurofibrillary degeneration that is characteristic of Alzheimer's disease.

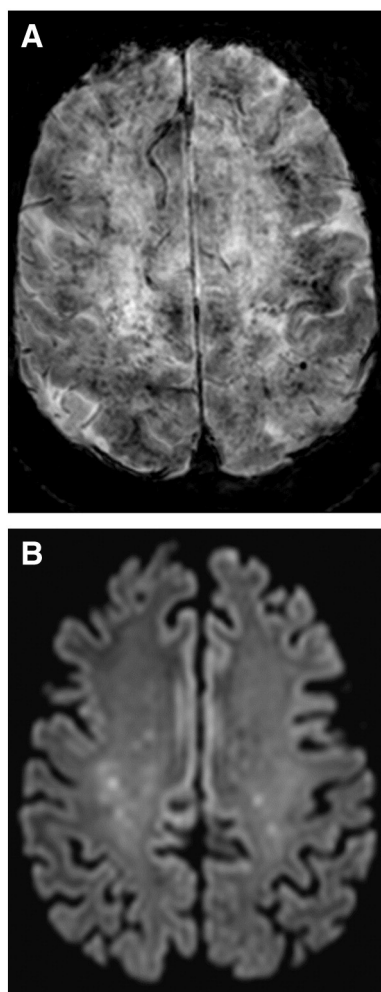


Fig. 2. Brain magnetic resonance imaging. A) Axial susceptibility-weighted image minIP recon showed tiny multiple hypointense points located on bilateral subcortical white matter. This is caused by the important difference of susceptibility between fat emboli and adjacent parenchyma. B) Axial diffusion-weighted image showing multiple hyperintense foci in both centrum semiovale relating to acute ischemic lesions.

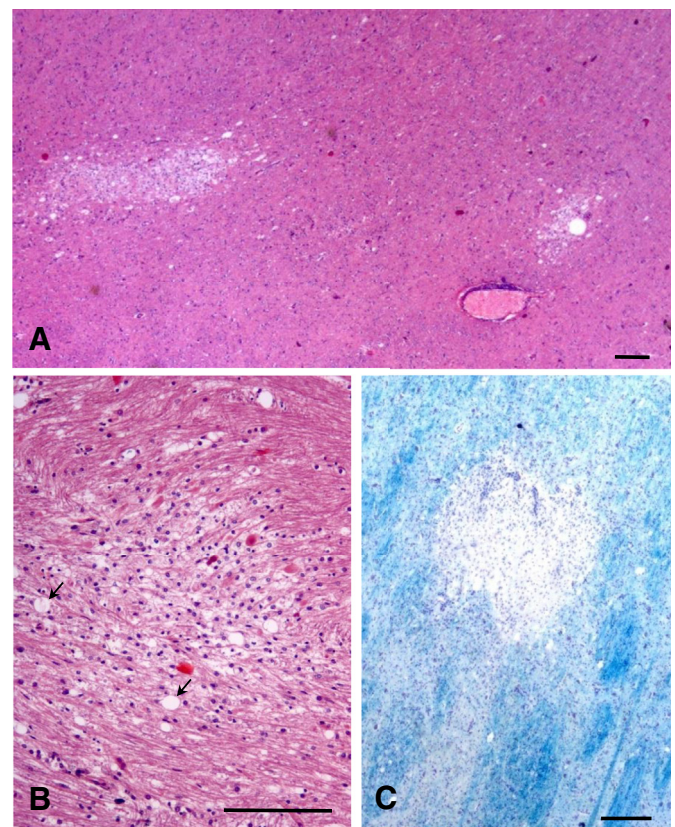


Fig. 3. Histologic findings. A) Multiple infarcts affecting especially dorsomedial thalamic nuclei. B) Detail of a subacute microinfarct with histiocytes, gliosis, and axonal swelling. Note the occasional white structures corresponding to fatty emboli (arrows). C) Several demyelinated lesions are revealed with Klüver–Barrera stain for myelin. Scale bars = 100 mm.

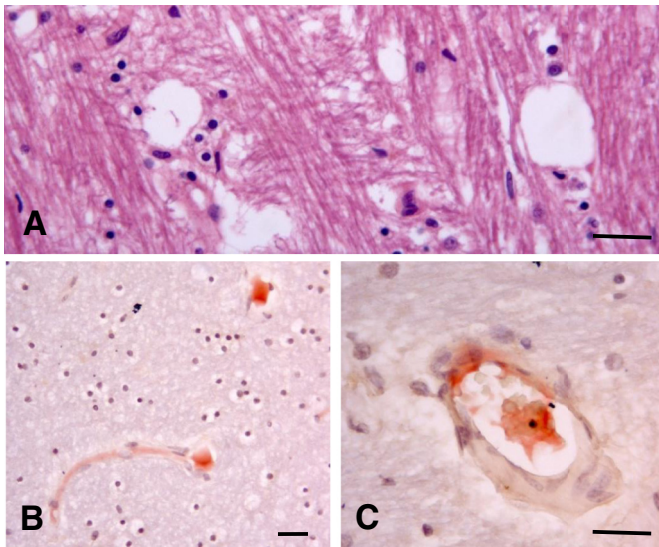


Fig. 4. Histologic findings. A) Micrograph of the thalamus exhibiting fatty emboli with hematoxylin–eosin staining, corroborated in red color with Oil Red O for detecting fat (B and C). Scale bars = 20 mm. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

3. Discussion

Neurological manifestations are common in patients with FES. The neurological symptoms are usually nonlocalizing and range in severity from mild disorientation or changes in mental status to coma [4–6]. The majority of patients with FES exhibit symptoms in the first 48 h. The pathophysiological mechanisms of the neurological symptoms appear to be associated with the direct effects of fat emboli on the brain (mechanical theory) and severe hypoxia associated with FES-induced respiratory failure (biochemical theory). In the case described here, the second mechanism could be a more plausible cause of NCSE because it can explain generalized EEG anomalies. However, we cannot rule out that our patient had a secondarily generalized NCSE whose focal onset was no longer apparent. Of note, similar EEG patterns may be seen frequently in subjects with hypoxic–anoxic encephalopathy. Although cognitive decline occurs frequently after hip and knee surgery, it is usually mild and transient. Interestingly, in a recent study, intraoperative cerebral microembolism occurred universally, but it seems that it did

not significantly influence postoperative cognition [7]. To the best of our knowledge, this is the first case of sr-NCSE that occurred because of fat embolism. Super-refractory nonconvulsive status epilepticus is an epileptic condition that may be defined as NCSE that continues or recurs 24 h or more after the onset of general anesthesia, including those cases where NCSE recurs on the reduction or withdrawal of anesthetic therapy [8]. We employed a modified definition of that recently proposed by Shorvon for super-refractory SE in the 3rd London-Innsbruck Colloquium on SE [9]. Shorvon's [9,10] definition was concerned with tonic–clonic SE and not, for instance, NCSE nor *epilepsia partialis continua*.

Magnetic resonance imaging (MRI) has been reported to be the most sensitive means of diagnosing cerebral fat embolism. The typical findings on conventional MRI in the acute stage are multiple, small, scattered, hyperintense lesions on diffusion-weighted images and T2-weighted images that usually appear in the white matter and deep gray matter. These findings are generally considered to represent cytotoxic edema in acute cerebral infarcts from fat emboli occluding cerebral arterioles and some vasogenic edema caused by the breakdown of the blood–brain barrier. Susceptibility-weighted imaging (SWI) is a relatively new MR technique that is extremely sensitive for detecting small hemorrhagic lesions in the brain that is clearly much more sensitive than the other conventional MR techniques, including T2. Some recent papers about FES have demonstrated that SWI enables detecting innumerable, minute, or punctate foci of low signal intensity throughout the brain [11,12]. In our case, minute hypointense lesions on SWI were found predominantly in the cerebral and cerebellar white matter and in the splenium of the corpus callosum, which is in accord with the distribution of the petechiae in the autopsy. Therefore, the hypointense lesions detected by SWI were considered to be petechiae caused by fat embolism. The number of hypointense foci on SWI might affect the prognosis.

There is little evidence of lasting harm caused by NCSE. This is a crucial point in order to establish a proportionate and adequate treatment. Wasterlain et al. [13] mentioned informally their experience with three patients with NCSE but without prior epilepsy whose postmortem brain examination showed neuronal loss in the hippocampus, amygdala, and piriform cortex. Afterwards, Fujikawa et al. [14] observed widespread neuronal loss and reactive gliosis in three subjects who died after the onset of focal motor and electrographic status epilepticus without systemic complications. Fernández-Torre et al. [15] studied the hippocampus and amygdala of a patient without previous history of chronic epilepsy, who died after suffering from a long-lasting intractable focal

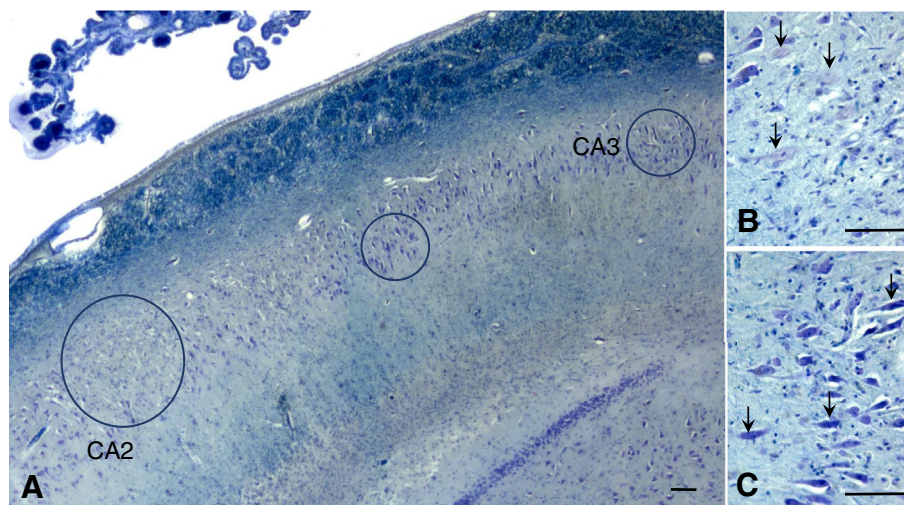


Fig. 5. Histologic findings. A) Dentate gyrus of the hippocampus at the CA2 and CA3 levels. B) Observe that in CA2, there is a chronic mesial sclerotic focus with gosh tangles (arrows in B) related with neurofibrillary degeneration that is characteristic of Alzheimer's disease. C) The two small circles (in A) are areas of recent injury with ischemic neurons. Observe that these two focal areas showing filiform neurons with reactive astrocytic gliosis background consistent with acute lesions are seen in CA3. Scale bars = 100 mm.

NCSE in coma, and noted neuronal loss, gliosis, and neuronal degeneration. Their findings supported the hypothesis that localization-related NCSE in the setting of acute brain disorders and coma might cause permanent hippocampal injury. Excitotoxicity is believed to be involved in production of the neuropathologic changes in NCSE. It is likely that cell damage is caused by excessive excitatory neurotransmitter release, which activates N-methyl-D-aspartate (NMDA) receptors, allowing calcium to enter the cell. Calcium and other ionic changes result in a cascade of biochemical changes that eventually lead to cell death [16].

In the present case, we did not find definitive histologic evidence of permanent neuronal damage as a consequence of NCSE. Although small scattered foci of acute lesions disclosing ischemic neurons were seen in CA3 of the hippocampus (Fig. 5), they were somewhat different from those described typically in status epilepticus. Unfortunately, we cannot be sure of the origin of these changes. These injuries could be a consequence of status epilepticus or result of the ischemia secondary to cerebral emboli. Of note, the EEG of our patient showed GPDs in keeping with generalized NCSE. It is well known that focal and generalized seizures arise from activation of different cerebral circuits, and it is also widely accepted that some subtypes of generalized NCSE as absence status epilepticus do not cause permanent neuronal damage nor cognitive impairment. It is possible that the maintenance of generalized epileptic activity, in this and other similar cases, depends on the overactivation of nonglutamatergic circuits. This could explain the discrete histopathologic changes seen in our patient.

4. Conclusions

This case shows that sr-NCSE should be considered a potentially fatal complication of FES. Nonconvulsive status epilepticus should be suspected in all those patients with unexplained diminution of consciousness level or in coma in the early postoperative period of orthopedic surgery. An urgent v-EEG evaluation is mandatory to obtain an accurate diagnosis, and continuous v-EEG monitoring will be helpful for treatment optimization and follow-up during status epilepticus.

Conflict of interest statement

None of the authors has any conflict of interest to disclose.

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