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CASE REPORT

Unexplained high lactate levels after long bone fractures: consider cerebral fat embolism syndrome

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Abstract

Cerebral fat embolism is an uncommon but serious complication of long-bone fracture. Nonetheless, recognition of this uncommon complication remains difficult. Here we present two cases of cerebral fat embolism syndrome (CFES) and describe a possible association between CFES and high lactate levels.

Introduction

Cerebral fat embolism is an uncommon but serious complication of long-bone fractures. The classic fat embolism syndrome (FES) is characterised by the clinical triad of respiratory insufficiency, altered mental status and petechiae. The frequency of post-traumatic FES is in the range of 0.7-0.9%.[1,2] FES typically manifests 24-72 hours after the initial insult. In general FES has a mild course; however severe cases are also known, with an estimated mortality up to 15%.[1] Cerebral involvement has frequently been reported and seems to aggravate the prognosis of FES. Clinical manifestations vary widely, from a simple alteration of vigilance, to seizures and coma. Despite the presence of several scoring systems, the diagnosis remains difficult.

Here we present two cases of cerebral fat embolism syndrome (CFES) and isolated high lactate levels without haemodynamic instability. An association between CFES and high lactate is discussed.

Patient A

A 26-year-old man was admitted to our hospital after being hit by a car. Due to nemaline myopathy, he was wheelchair and home ventilator dependent. On arrival he had a maximal Glasgow Coma Score (GCS). Conventional radiology revealed fractures of both femora and a fracture of the left tibia. Treatment was conservative.

The patient was admitted to our intensive care unit (ICU) and within a few hours, his consciousness decreased to a GCS of 3. At that time there were no signs of respiratory or haemodynamic insufficiency *(table 1)*. A CT scan showed a swollen brain with bilateral haemorrhagic contusions. An MRI, eight hours later, showed multifocal bilateral ischaemic areas both supratentorially and infratentorially and most pronounced in the basal nuclei, the deep white matter, the cortex and the cerebellum *(figure 1)*. Subsequently, his respiratory condition deteriorated quickly and despite the absence of a petechial rash, the clinical picture and MRI findings were most suspect for CFES. Although the patient showed no signs of sepsis, cardiac failure or ischaemia, our patient had a persistently elevated lactate level between 4.9-8.2 mmol/l *(figure 2)*.

Based on his past medical history and the likely poor prognosis of CFES, the treatment was stopped. The patient died within 48 hours after admission to our hospital.

Patient B

A 19-year-old man presented with multiple trauma after a car accident. Besides a contained rupture of the aorta and a grade 1 spleen laceration, he had multiple fractures of the sacrum and femora on both sides and a fracture of the right lower leg. A CT scan of the brain on admission showed no abnormalities. The patient underwent surgery and a total of three external fixators were placed on both legs followed by an immediate thoracic endovascular aortic repair (TEVAR).

Afterwards the patient was admitted to our ICU, and sedatives were discontinued for neurological follow-up. The patient had a maximal Eye and Motor score while still on the ventilator. Several hours later he rapidly lost consciousness and within 20 minutes his GCS was 3, while brain stem reflexes remained intact. An EEG showed no signs of epilepsy and the CT scan showed diffuse brain oedema without vascular abnormalities *(figure 3)*. Within a few hours the pulmonary condition of our

Table 1. Vital signs since the time of ICU admission

	T = 0	2	4	6	8	10	12	14	16	18	20	24	26	28	30	32	34	36	38	40	42	44	46
Patient A	HR	129	128	116		123	120		110	120	120	122											
	MAP [mmHg]	62	80	88		75	83		74	70	65	58											
	SpO2 [%]	100	94	100	100	100	100		100	100	100	100											
	Temperatuur [°C]	34,8		36		36,5			36,3	36,4	36,4	36,3											
	CO [L/min]																						
	CI [L/min/m^2]																						
	Urine [ml]	360		300		180	70		90	60	15	15											

Patient B	HR		110	128	143	135	130	122	124	121	121	130	129	134	133	137	133	132	121	114		120	133
	MAP [mmHg]		77	71	80	73	54	60	64	67	69	84	78	73	72	70	70	66	67	73		93	103
	SpO2 [%]		100	100	97	92	97	97	97	96	95	93	92	90	91	90	90	90	94	93	93	95	93
	Temperatuur [°C]		35,7	37	39	39	38,9	37,5	36,9					39,2	39,5	39,7	39,4	38,9	38,7	38,6	38,6		38,5
	CO [L/min]									7,57					7,56		7,41						
	CI [L/min/m^2]									3,47					3,47		3,4						
	Urine [ml]	400	280	280	110	100	90	75	90	60	70	85	185	60	140		220	270	200		320	340	320

HR = heart rate; MAP = mean arterial pressure; Sp02 = peripheral capillary oxygen saturation; CO = cardiac output; CI = cardiac index

Figure 1. MRI of patient A. Multifocal bilateral ischaemic areas both supratentorially and infratentorially and most pronounced in the basal nuclei, the deep white matter, the cortex and the cerebellum, consistent with a 'starfield' pattern

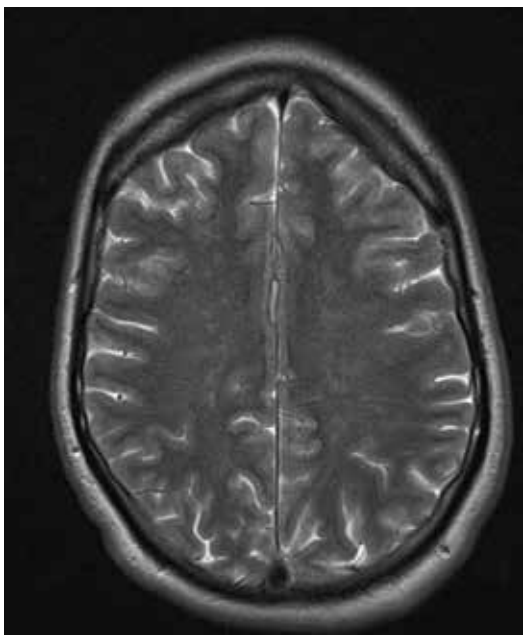
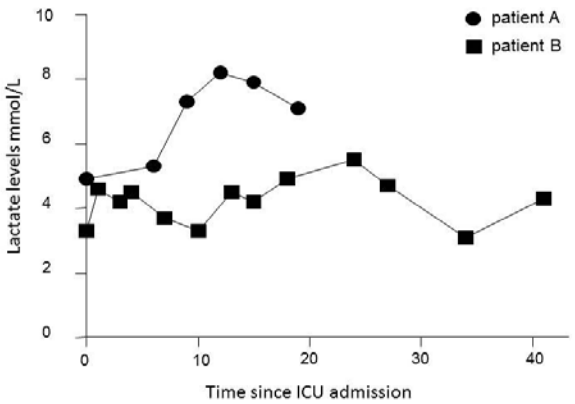


Figure 2. Lactate levels in our patients from the time of ICU admission



patient deteriorated quickly with both oxygenation as well as ventilation abnormalities. Given the neurological signs in combination with the pulmonary deterioration, a diagnosis of fat embolism syndrome was suspected. Although there were no signs of sepsis, cardiac failure *(table 1)*, or local ischaemia, our patient had an isolated lactate level of 3.1-5.5 mmol/l *(figure 2)*. Given the poor respiratory condition of the patient, and the clinical picture, we did not perform an MRI.

In the following hours the patient's neurological condition worsened, brain stem function deteriorated and treatment was finally stopped. The patient died within 48 hours after admission to our hospital.

Figure 3. CT scan of patient B. Diffuse brain oedema. Grey-white matter differentiation lost in both the frontal part of the brain as well as in the basal nuclei

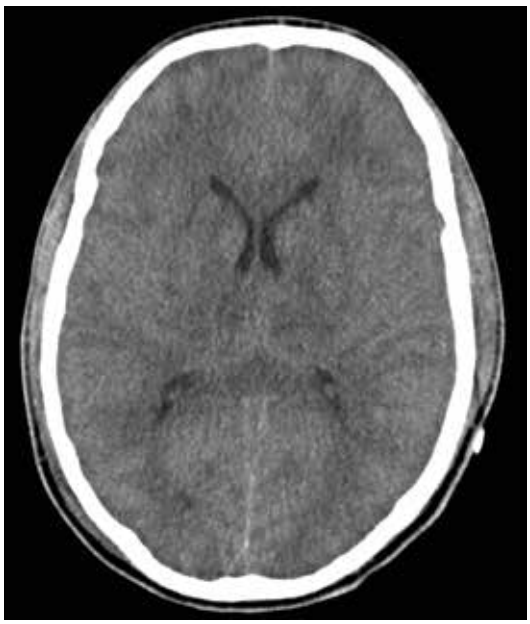
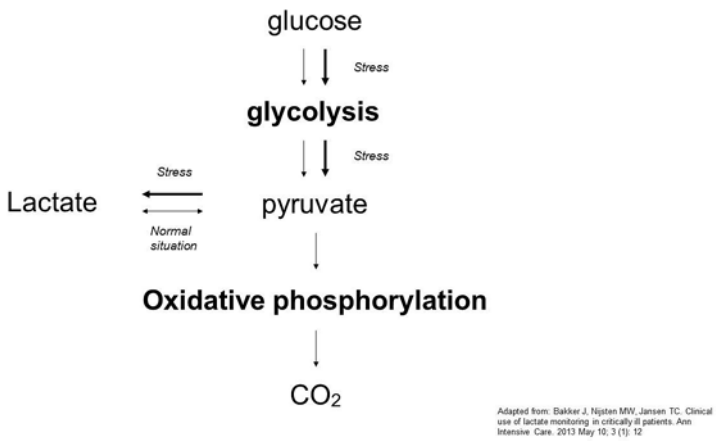


Figure 4. Glucose-lactate-pyruvate association



Adapted from Bakker J, et al.[6]

Table 2. Criteria to diagnose FES

Gurd's criteria [3]		Schonfeld criteria [4]	Score	Lindegue criteria [5]
Major criteria	Petechiae	Petechiae	5	Sustained pO2 < 8 kPa
	Hypoxemia	X-ray chest diffuse infiltrates	4	Sustained pCO2 > 7.3 kPa
	Altered mentality	Hypoxemia	3	Sustained respiratory rate > 35/min, inspite of sedation
		Fever	1	Increases work of breathing, dyspnoea, tachycardia, anxiety
Minor criteria	Tachycardia	Tachycardia	1	
	Fever	Tachypnoea	1	
	Thrombocytopenia	Confusion	1	
	Anaemia			
	Anuria or oliguria		FES > 5	
	Retinal embolism			
	Fat globule in urine or sputum			
	Jaundice			
	High erytrocyte sedimentation rate			

Discussion

FES remains a difficult diagnosis despite the development of several scoring systems including the criteria of Gurd[3], Schonfeld,[4] and Lindegue[5] *(table 2)*. Here we suggest that increased lactate levels in the absence of haemodynamic instability and a compatible clinical picture could point to a diagnosis of CFES.

Lactate is a metabolite of the two main energy processes: glycolysis and oxidative phosphorylation. Under normal conditions, glucose undergoes glycolysis to form pyruvate, which in turn is converted during oxidative phosphorylation into CO_2, generating 36 adenosine triphosphate (ATP) molecules. However, in situations of increased energy demand (e.g. stress, trauma, etc.) the rate of glycolysis increases far more than the oxidative phosphorylation can process and pyruvate is mainly converted into lactate, generating only two ATP molecules. During the recovery phase lactate is then converted back into pyruvate, demonstrating that lactate may act as a critical energy buffer in these situations. Therefore, increased glycolysis may be an important cause of hyperlactataemia *(figure 4)*.[6]

Although glucose is assumed to be the main energy source for all living tissues, there is accumulating evidence that lactate, and not glucose, is preferentially metabolised by neurons in the brain. Under physiological, but also pathological conditions, lactate is an important metabolic precursor for cerebral gluconeogenesis and ATP production.[7] During cerebral activation the plasma lactate increases and the brain takes up lactate in proportion to the arterial concentration. This may serve to satisfy greater demands for energy substrate from the brain.[8] The cerebral lactate uptake, together with glucose uptake, exceeds the concomitant oxygen uptake, as reflected by the decrease in the cerebral metabolic ratio from a resting value of 6 to <2.[9] Under these conditions, lactate can be an 'opportunistic', glucose-sparing substrate when present in high amounts. Although most evidence supports glucose as the major fuel for a normal activated brain, recent insights suggest that an increased arterial lactate might protect the injured brain.[10] In addition, the administration of exogenous lactate exerts significant neuroprotection in animals and lactate transport is essential for long-term memory formation.[11]

Recent findings suggest that, not only the activated brain, but also the injured brain takes up lactate, which is subsequently oxidatively metabolised. Lactate uptake occurs despite relatively high brain lactate levels after traumatic brain injury (TBI) suggesting up-regulation of monocarboxylate transporters, responsible for lactate uptake. As glucose delivery to brain cells seems to be maintained during periods of lactate uptake, lactate uptake may reflect an adaptive response to the increased energy demands and change in metabolic priorities of the injured brain.[8] Besides uptake, the brain also produces lactate. Animal studies suggest that the elevated lactate levels found after brain injury are the result of the production of lactate in brain tissue, cerebral spinal fluid (CSF), and blood, which increase in proportion to the severity of the injury. Initially, the lactate levels in blood and CSF increase immediately following trauma while brain lactate gradually increases. It is speculated that the initial elevation of CSF lactate reflects the systemic response of trauma, and the secondary rise of CSF lactate levels following severe trauma is due to slow seepage of lactate produced by brain tissue into the CSF space.[11] Moreover, it is hypothesised that diffuse damage to the brain prevents the neurons from using lactate whereas astrocytes and oligodendrocytes keep producing lactate resulting in a net increase in lactate levels.[12] Furthermore, there is a difference between lactate produced by hyperglycolysis (due to aerobic metabolism, corresponding to energy demands and neuronal cell survival) and hypoxia-induced lactate production (secondary to anaerobic metabolism, resulting from cell energy failure and neuronal loss), indicating that lactate may be used as an aerobic substrate by the injured human brain.[13]

During TBI increases in lactate levels have been described. In a recent study in 89 patients with TBI, the lactate levels were 3.5 ± 2.0 mmol/l, with an increase in the lactate/pyruvate ratio of 37.7 ± 25.9. In this study, elevated lactate levels as part of metabolic crises was a strong independent predictor of poor outcome at six months following trauma.[7] With the use of cerebral microdialysis (CMD) it was recently shown that in humans with TBI, brain lactate levels increase up to 4.8 mmol/l (normal values 2.7 ± 0.9 mmol/l).[13] Also during subarachnoid haemorrhage elevated lactate levels have been described. In 54% of patients with subarachnoid haemorrhage, the CMD lactate was >4 mmol/l. In these patients elevated CMD lactate was associated with a poor outcome when the source of lactate elevation was hypoxia rather than hyperglycolysis.[14]

A review of the literature revealed 54 cases of CFES between 1980 and 2012. A good outcome (intact or mild disability) was seen in 57.6% of patients with coma. Although publication bias is probably present, these data caution against overt pessimism.[15]

Here we speculate that diffuse brain injury due to CFES increases brain lactate levels and subsequently plasma lactate levels. Although we cannot exclude another source of lactate production, both our patients were haemodynamically stable and showed no other signs of local ischaemia. One could argue that increases in brain lactate due to CFES are probably caused by diffuse hypoxia rather than hyperglycolysis, which might also have prognostic value as seen during TBI and SAH.

Conclusion

Cerebral fat embolism syndrome is an uncommon but serious complication of long-bone fractures. Although several scoring systems have been developed to diagnose (C)FES, clinical recognition remains difficult. Here we suggest that when a trauma patient presents with long-bone fractures, followed by neurological deterioration and increased lactate levels, one should consider a diagnosis of CFES.

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Disclosure

The authors declare no conflict of interest.