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RESEARCH

Multisystemic involvement of post-traumatic fat embolism at a Pediatric Trauma Center: a clinical series and literature review

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Abstract

Post-traumatic fat embolism syndrome (FES) is a severe complication consequent to bone fractures. The authors describe its clinical features and management in a population of teenagers by detailing demographics, organ involvement, laboratory, and imaging findings, as well as outcome. Moreover, a systematic review of pediatric published case reports of post-traumatic FES is provided. First, a series of eight episodes of post-traumatic FES that occurred in seven patients (median age 16.0 years, IQR 16.0–17.5) admitted to a pediatric intensive care unit (PICU) in an 8-year period was analyzed through a retrospective chart review. Secondly, a systematic research was performed on PUBMED database. Trauma patients ≤ 18 years without comorbidities in a 20-year period (2002–2022) were included in the review. Neurological impairment was present in five out of seven patients, and a patent foramen ovale was found in four cases. Hemodynamic instability requiring vasoactive drugs was recorded in four patients. A severe form of acute respiratory distress syndrome (ARDS) occurred in five cases, with the evidence of hemorrhagic alveolitis in three of them. In the literature review, eighteen cases were examined. Most cases refer to adolescents (median age 17.0 years). More than half of patients experienced two or more long bone fractures (median: 2 fractures). Both respiratory and neurological impairment were common (77.8% and 83.3%, respectively). 88.9% of patients underwent invasive mechanical ventilation and 33.3% of them required vasoactive drugs support. Neurological sequelae were reported in 22.2% of patients.

Conclusion: Post-traumatic FES is an uncommon multi-faceted condition even in pediatric trauma patients, requiring a high level of suspicion. Prognosis of patients who receive prompt support in an intensive care setting is generally favorable.

What is Known:
- *Post-traumatic fat embolism syndrome is a severe condition complicating long bone or pelvic fractures.*
- *Little is known about clinical features and management in pediatric age.*

What is New:
- *Post-traumatic fat embolism syndrome can cause multiple organ failure, often requiring an intensive care management.*
- *Prompt supportive care contributes to a favorable prognosis.*

Keywords Pediatric trauma · Fat embolism · Brain injury · Respiratory failure

Abbreviations

ARDS	Acute respiratory distress syndrome
CPC	Cerebral performance category
CT	Computerized thomography

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FES	Fat embolism syndrome
GCS	Glasgow coma scale
HMG-CoA	3-Hydroxy-3-methylglutaryl-coenzyme A
MRI	Magnetic resonance imaging
PICU	Pediatric intensive care unit

Introduction

Post-traumatic fat embolism syndrome (FES) represents a severe complication which mostly involves patients suffering from long bone or pelvic fractures. Respiratory insufficiency, neurologic changes, and a skin petechial rash (within 72 h from trauma) are typical signs, but fever, tachycardia, retinal artery occlusion, jaundice, hematuria, and oliguria may also occur. Even though several diagnostic criteria have been proposed in order to aid in the diagnosis [1–3], this medical condition still poses a major diagnostic challenge for most clinicians. The most commonly used diagnostic tool is those proposed by Gurd [1], which includes three major and minor criteria; diagnosis of FES is made by the presence of at least two major, or one major and four minor criteria. More recently, Schonfeld suggested a semi-quantitative means for diagnosis of FES, based on seven clinical variables [2]: according to this index, a score above 5 is indicative of FES (Table 1). Since a specific diagnostic tool for pediatrics has not yet been developed, the above descripted criteria are commonly used in clinical practice ever for patients under 18 years old.

Besides primary embolization from initial trauma, orthopedic surgery involving manipulation of intramedullary canal, such as nail placement, may result in additional fat embolism. Indeed, its prevalence appears to increase in bilateral femoral fractures and after intramedullary nail fixation [4]. When a multisystemic involvement is present, the overall syndrome's mortality can reach 10–20%, as reported in historical series [5], though decreasing with modern intensive care availability. Post-traumatic FES is reported among adult patients with a prevalence of 1–2%, while it is relatively uncommon also in high-volume pediatric trauma centers [6], where adolescents are referred, so that a deep investigation about the clinical course and management of post-traumatic FES in pediatric intensive care unit (PICU) is not reported in literature. A possible explanation could be found, apart from the higher cellularity in childhood, in the different composition of children's fat marrow, which contains less olein and more palmitin and stearin [7].

Literature reports regarding the clinical management of post-traumatic FES in pediatrics are limited to single experiences depicted in case reports or as a part of larger series including adult patients. In this paper, we discuss eight episodes of post-traumatic FES occurring in seven patients admitted to our PICU over an 8-year period. Moreover, by reviewing the recent literature about this topic, we highlight clinical features, diagnostic workout, in-hospital course, and outcome of children affected by post-traumatic FES, with the aim to define its potential to result in life-threatening complications.

Table 1 Gurd's criteria and Schonfeld's fat embolism index

Gurd's criteria [1]	
Major	
Petechial rash	
Respiratory symptoms with radiographic changes	
Central nervous system signs unrelated to trauma or other condition	
Minor	
Tachycardia	
Fever > 38 °C	
Retinal changes (fat or petechiae)	
Renal abnormalities (oliguria, anuria, lipiduria)	
Acute thrombocytopenia	
Acute decrease in hemoglobin	
High erythrocyte sedimentation rate	
Fat globules in sputum	
Schonfeld's fat embolism index [2]	
Symptoms and signs	**Points**
Petechial rash	5
Alveolar infiltrates	4
Hypoxemia (PaO_2 < 70 mmHg)	3
Confusion	1
Fever > 38 °C	1
Tachycardia	1
Tachypnea	1

Materials and methods

This single-center retrospective cohort study was approved by the local Institutional Review Board (Prot. 30,870/19) on September 12, 2019. The need for individual informed consent was waived due to retrospective nature of the study. The study was carried out according to institutional and Good Clinical Practice (GCP) guidelines. Results of the retrospective analysis are reported in accordance with the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) statement, while the systematic review was designed according to the PRISMA (preferred reporting items for systematic reviews and meta-analyses) procedure.

A retrospective review of our institutional PICU trauma registry was performed. An 8-year period (2013–2020) was considered, during which 642 patients, aged from 0 to 18 years, had been admitted to the PICU with a diagnosis of trauma. After clinical suspicion of FES had been raised, the diagnosis was confirmed by referring to Gurd's criteria [1] and Schonfeld's fat embolism index [2] and ruling out possible alternative diagnoses by lung and brain imaging. Accordingly to Gurd's criteria, in patients admitted in PICU after trauma, diagnosis of fat embolism was made by the presence of at least two out of three major signs, including neurologic abnormalities, respiratory insufficiency and skin petechial rash, or, alternatively, by the presence of one major and at least four minor criteria, and the absence of an alternative explanation [8]. Data recorded from chart review include demographic information, type of fracture, time from injury to symptoms onset, clinical signs, neurological status (through Glasgow coma score), laboratory and imaging findings, and outcome. Moreover, information about respiratory failure (level of hypoxemia, type and length of mechanical ventilation, presence of hemorrhagic alveolitis) was reported. In addition, a systematic research of the literature reporting post-traumatic fat embolism in PubMed database in the last 20 years (2002–2022) was conducted: the search terms were "fat embolism", "fat embolism AND child", and "fat embolism AND adolescent", and the results were filtered by age (birth–18 years). All the studies which provided a partial or complete clinical description of post-traumatic FES were included in the review. Only studies involving patients without comorbidities were included in the analysis. Data collected from the review included age, sex, number of long bone fractures, time of onset of symptoms, onset before or after surgery, worst Glasgow coma scale (GCS), worst PaO_2/FiO_2, brain and chest imaging, use of vasoactive drugs, Gurd's criteria, presence of patent foramen ovale, PICU length of stay, days of mechanical ventilation, need for tracheostomy, use of additional treatments beyond vital function support and neurological outcome through the cerebral performance category (CPC) score. In case some data were missing, they were coded as "NR" (not reported).

Data were collected and analyzed using a Microsoft Excel 2016 spreadsheet (Microsoft Corporation, Redmond, USA). Median and interquartile range (IR) were given for metric variables, while frequencies and percentages were given for non-metric variables. The study was approved by the local Ethical Committee.

Results

Patients' clinical characteristics, radiological findings, therapeutic approach, and clinical course in PICU, including neurological and cardiovascular complications, are depicted in Fig. 1 and Table 2, while a focus on respiratory features and management is reported in Table 3. Family history was unremarkable for all patients.

Median age of the seven patients was 16.0 years (IQR 16.0–17.5). Median time of symptoms onset was 24 h (IQR 19–24 h) and median GCS at presentation was 11 (IQR 7.75–15). FES occurred after surgery in patient #1, who

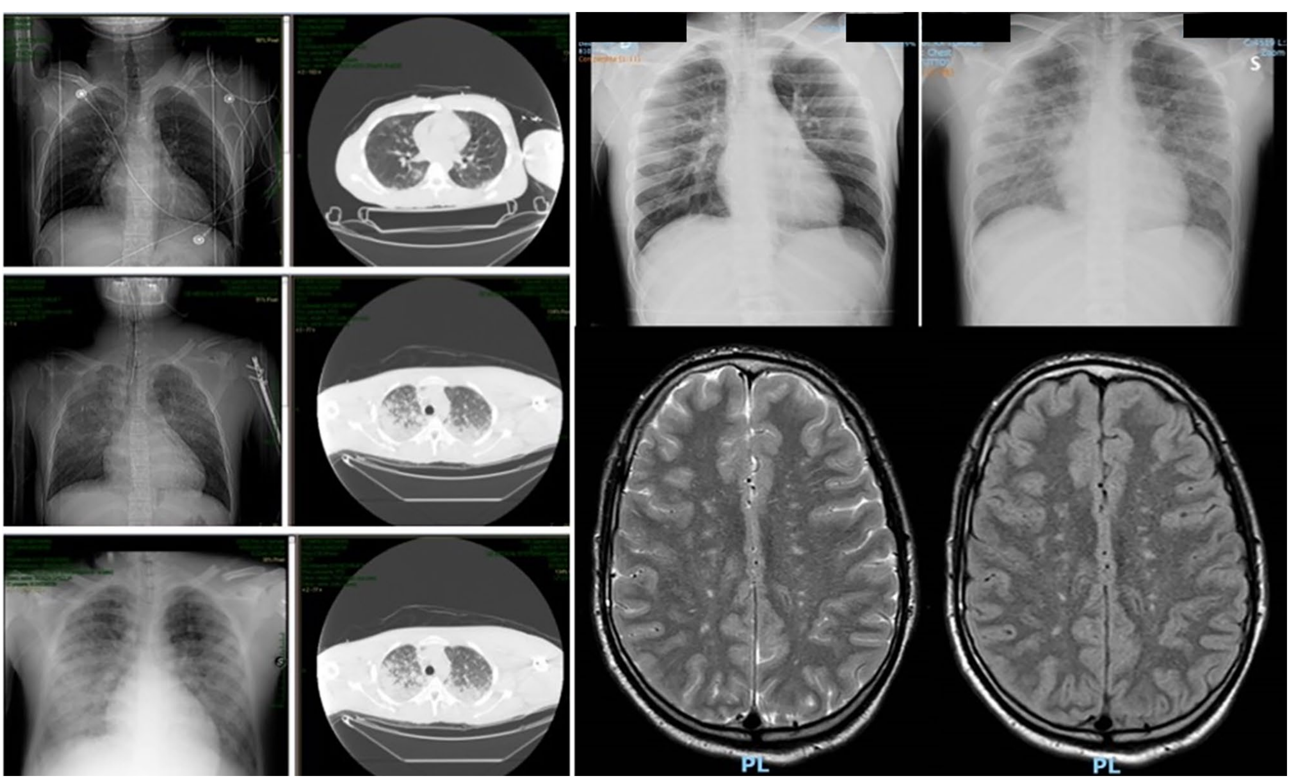

Fig. 1 Diagnostic imaging of patient #1 (left) and patient #5 (right) of the clinical series

Table 2 Characteristics and clinical course of the seven patients admitted to PICU for post-traumatic FES, including laboratory values and treatment

Patient	#1	#2a	#2b	#3	#4	#5	#6	#7
Age in years/gender	16/male	17/female	17/female	15/female	16/male	16/male	18/male	18/male
Bone fractures	Clavicle, pelvis, sacrum, left femur, left tibia, left fibula	Left femur, left tibia, left fibula	Left femur, left tibia, left fibula	Right femur	Right femur	Right femur	Left acetabulum, left femur, left tibia, left fibula	Bilateral femur, left ulna
Associated injuries	None	Lung contusions	None	Lung contusions	None	None	Maxillo-facial	None
Gurd's major criteria	R, P	C, R, P	R	R, P	C, R	C, R, P	C, R, P	C, R, P
Gurd's minor criteria	Renal signs, increasing ESR, fat present in urine, drop in Ht/PLT	Fever, renal signs, increasing ESR, drop in Ht/PLT	Tachycardia, fever, renal signs, retinal changes, increasing ESR, fat present in urine, drop in Ht/PLT	Tachycardia, fever, increasing ESR, drop in Ht/PLT	Tachycardia, renal changes	Fever, retinal changes, increasing esr, drop in ht/plt	Tachycardia, fever	Fever, retinal changes
Schonfeld's fat embolism index	13	15	6	11	10	15	16	11
Onset (hours from trauma)	18 h	20 h	11 days relapse	48 h	24 h	24 h	12 h	24 h
Onset after surgery	Yes	No	Yes	No	No	No	No	Yes
Closed reduction before onset	No	Yes	-	Yes	Yes	Yes	Yes	No
Neurological status	GCS 15	GCS 8	GCS 15	GCS 15	GCS 13	GCS 7 + left paresis	GCS 5	GCS 9
Brain imaging CT scan MRI	Normal	-	-	-	Minimal focal lesions	Normal Multiple focal ischemia	Normal Multiple focal ischemia	Normal Multiple focal ischemia
Hemodynamic support	NEPI + DOB	-	NEPI + DOB	-	DOB + DOP	-	NEPI	-
Patent forame ovale	-	-	-	-	+	+	+	+
Outcome	Recovery	Recovery; transient peripheral neuropathy	Recovery	Recovery	Recovery	Recovery (delayed)	GOS 3, tracheostomy, autonomic dysregulation	Recovery

R Respiratory, *C* cerebral, *P* petechiae, *ESR* erythrocyte sedimentation rate, *Ht* hematocrit, *PLT* platelets, *GCS* Glasgow coma scale, *NEPI* norepinephrine, *DOB* dobutamine, *DOP* dopamine, *GOS* Glasgow outcome scale

Table 3 Pulmonary features and respiratory support in patients admitted to PICU with post-traumatic FES

Patient	#1	#2a	#2b	#3	#4	#5	#6	#7
ARDS (according to Berlin definition) [9]	Severe	Severe	Severe	Moderate	Severe	Severe	No	No (transient hypoxemia)
Hemorrhagic alveolitis	+	-	+	-	-	+	-	-
MinPaO_2/FiO_2	68	98	81	175	75	85	102	251
MV (hours)	162	192	240	-	168	170	276	24
IMV mode	PRVC	VC	VC	-	VC	VC	VC, PSV	PSV
NIV yes/no (hours)	Yes (48)	Yes (5)	Yes (29)	Yes (96)	No	Yes (48)	No (tracheo-stomy)	No
NIV mode	TF NPPV	TF NPPV	Helmet CPAP	TF NPPV	-	TF CPAP	-	-
Chest radiological findings	Chest CT scan: Interstitial-alveolar bilateral infiltrates	Chest CT scan: interstitial-alveolar basal infiltrates, pulmonary contusions	Chest CT scan: Pulmonary consolidation, bilateral pleural-pericardial effusion	Chest CT scan: defects of filling of the LLL, RL consolidation, contusion areas	CXR: diffuse opacities	Chest CT scan: bilateral ground-glass opacity	CXR: interstitial-alveolar bilateral infiltrates	CXR: normal

ARDS Acute respiratory distress syndrome, *MV* mechanical ventilation, *IMV* invasive mechanical ventilation, *PRVC* pressure regulated volume control, *VC* volume control, *PSV* pressure support ventilation, *TF* total face, *NPPV* noninvasive positive pressure ventilation, *CPAP* continuous positive airway pressure, *CT* computerized tomography, *CXR* chest X-ray, *LLL* left lower lobe, *RL* right lung

underwent intramedullary nail fixation of humeral fracture and external fixation for the other fractures, and in patient #7, who underwent intramedullary nail fixation for ulnar and femoral fractures. All the other patients underwent close fracture reduction and developed FES before surgery. After fat embolism had occurred, first step of surgery always consisted in external fixation. All patients were considered at high risk for venous thromboembolism and received appropriate DVT prophylaxis. Lower extremity venous echo color Doppler scan was performed in all patients within the first 24 h after FES diagnosis, resulting always negative. Vasoactive drugs were required in four out of eight episodes (50.0%). Six episodes (75.0%) were characterized by the occurrence of an acute respiratory distress syndrome (ARDS), according to the Berlin definition [9]: in these patients, the minimum PaO_2/FiO_2 had a median value of 83 (IQR 76.5–94.75), and the median duration of mechanical ventilation was 170 h (IQR 168–192 h) (Table 3). Seven out of eight teenagers (87.5%) had a favorable outcome while, in one patient, a severe neurological deficit (i.e., decerebrate posturing and dysautonomia) persisted 1 month after trauma.

As a second step, 152 articles were screened, and a total of 18 research studies, describing 19 clinical episodes of fat embolization, were identified and included in the review (Table 4) [10–27]. All episodes but one occurred in adolescents (median age 17.0 years, male 55.6%) and symptoms consistent with FES appeared on median 18 h after trauma. Most patients presented neurological ($n=14$, 77.8%) and/or respiratory ($n=15$, 83.3%) involvement, as found on cerebral and/or chest imaging, whereas other symptoms were less common. Use of vasoactive drugs was reported in six out of eighteen cases (33.3%). More than half of patients experienced two or more long bone fractures (median: 2 fractures). In reports in which a patent foramen ovale was actively sought, it was found in 16.7% of cases. Additional/unusual treatments were reported in 38.9% of the clinical experiences: in particular, statins and inhaled nitric oxide were used in three cases, while one patient required cardiopulmonary resuscitation, another one underwent decompressive craniectomy and the only infant of the series underwent high-frequency oscillatory ventilation and continuous renal replacement treatment. Invasive mechanical ventilation was often necessary (median length: 14 days; reported in 10 out of 18 studies) and tracheostomy was performed in four patients (22.2%). No fatalities were evidenced in the review. Fourteen patients were discharged with a good cerebral performance, while a severe cerebral disability remained in one patient.

Discussion

The release of fat globules into the peripheral circulation is a known complication of blunt force injuries, especially acting on pelvic or long bone fractures [28]. Two theories are postulated for the occurrence of FES. The mechanical theory states that elevation of intramedullary pressure due to trauma facilitates the release of large fat droplets into the venous system [29]; consequently, fat globules can reach

Table 4 Review of literature reports of post-traumatic fat embolism syndrome in pediatrics

ID	Age/gender	Long bone fracture (n°)	Onset (hours after Trauma)	Onset after surgery	GCS	Brain imaging	Chest imaging	Worst PaO_2/FiO_2	Need for vaso-active drugs	Gurd's maior criteria	Gurd's minor criteria	Patent foramen ovale	Additional treatments	PICU length of stay (days)	IMV days	Tracheostomy	CPC
Ostlie et al. [10]	16/M	2	24	No	7	MRI: multifocal lesions	CT: interstitial thickening, bilateral ground-glass opacities	NR	No	C, R	Fever, tachycardia, anemia, LPC, renal signs, jaundice	no	Statins, iNO	6	2	No	1
Millen et al. [11]	17/F	6	4	Yes	7	CT: cerebral edema MRI: multifocal lesions	NR	NR	Yes	C, R	Tachycardia, anemia	NR	Decompressive craniectomy	NR	NR	No	2
O'Neill et al. [12]	17/M	2	12	Yes	NR	NR	CXR: bilateral interstitial opacities CT: scattered ground-glass opacities	NR	NR	C, R	Fever	NR	-	NR	2	No	1
Huffman et al.[a] [13]	15/M	1	18	No	NR	NR	Normal	NR	Yes	R	Tachycardia, anemia, LPC	NR	CPR	2	1	No	1
Aggarwal et al. [14]	18/M	1	24	Yes	NR	NR	CXR: normal	NR	NR	P, C, R	Fever, renal signs, LPC	NR		30	25	Yes	1
Molière et al. [15]	18/M	1	6	Yes	14	MRI: multifocal lesions	CT: diffuse ground-glass opacities	NR	Yes	C, R	-	NR	-	NR	NR	No	1
Whalen et al. (1) [16]	17/M	2	10	Yes	8	CT: negative	CXR: bilateral diffuse infiltrates	58	NR	C, R	-	No	-	-	-	-	-
Whalen et al. (2) [16]	17/M	2	34	No	4 T	MRI: multifocal lesions	NR	NR	NR	C, R	LPC, renal signs, retinal changes	No	Statins	NR	NR	Yes	2

Table 4 (continued)

ID	Age/gender	Long bone fracture (n°)	Onset (hours after Trauma)	Onset after surgery	GCS	Brain imaging	Chest imaging	Worst PaO_2/FiO_2	Need for vaso-active drugs	Gurd's maior criteria	Gurd's minor criteria	Patent foramen ovale	Additional treatments	PICU length of stay (days)	IMV days	Tracheostomy	CPC
Nawaf et al. [17]	16/M	2	14	Yes	14	NR	CT: bilateral ground-glass opacities	NR	no	C, R	-	No	-	4	0	No	1
Honda et al. [18]	16/F	1	9	No	14	MRI: multifocal lesions	CT: pulmonary contusion	285	no	C, R	Fever, tachycardia	No	Statins	NR	NR	No	1
Amigoni et al. [19]	1/F	1	48	No	NR	NR	CXR: bilateral diffuse opacities	50	yes	R	Fever, tachycardia, renal signs, fat globules	No	HFOV, iNO, CRRT	NR	19	No	1
Hufner et al. [20]	16/F	1	20	No	7	MRI: multifocal lesions	CXR: bilateral interstitial opacities	NR	NR	P, C,	Tachycardia, renal signs, retinal changes	No	-	NR	NR	No	1
Meyer et al. [21]	18/M	6	24	No	4	CT: multiple bilateral hypodensi-ties MRI: multifocal lesions	CXR: Bilateral patchy opacities	NR	NR	C	Fever, tachycardia, anemia, retinal changes	No	-	NR	22	No	1
Özyurt et al. [22]	16/F	2	18	Yes	4	CT: cerebral edema	CXR: Bilateral diffuse opacities	63	Yes	P, C, R	Anemia, LPC	Nr	-	13	10	Yes	1
Butteriss et al. [23]	18/F	2	12	No	3	CT: negative MRI: multifocal lesions, cytotoxic oedema	NR	NR	NR	C, R	-	No	-	NR	21	No	2
Van den Brande et al. [24]	18/F	5	24	No	NR	NR	CT: Bilateral ground-glass opacities, centrilobular and subpleural nodules	NR	Yes	C, R	Fat globules	No	iNO	NR	18	No	3

Table 4 (continued)

ID	Age/gender	Long bone fracture (n°)	Onset (hours after Trauma)	Onset after surgery	GCS	Brain imaging	Chest imaging	Worst PaO_2/FiO_2	Need for vaso-active drugs	Gurd's major criteria	Gurd's minor criteria	Patent foramen ovale	Additional treatments	PICU length of stay (days)	IMV days	Tracheostomy	CPC
Nastanski et al. [25]	17/M	2	12	Yes	4	CT: negative MRI: multifocal lesions	NR	NR	NR	C		Yes	-	NR	NR	Yes	1
Malagari et al. [26]	17/M	1	48	NR	15	NR	CT: Ground-glass, septal thickening	323	NR	P, R	Tachycardia, renal changes	NR	-	NR	NR	No	1
Forteza et al. [27]	17/F	1	14	Yes	13	MRI: multifocal lesions	NR	NR	NR	P, C, R	Tachycardia	Yes	-	NR	NR	No	1

GCS Glasgow coma scale, *IMV* invasive mechanical ventilation, *CPC* cerebral performance category scale, *MRI* magnetic resonance imaging, *CT* computerized tomography, *C* cerebral, *R* respiratory, *LPC* low platelet count, *iNO* inhaled nitric oxide, *CXR* chest X-ray, *CPR* cardiopulmonary resuscitation, *P* Petechiae, *HFOV* high-frequency oscillatory ventilation, *CRRT* continuous renal replacement therapy

[a]Embolization during surgery

the pulmonary vessels and, through arteriovenous shunts or a patent foramen ovale, pass into the systemic circulation, thus producing systemic effects on end-organs, such as brain, skin or kidneys. This theory provides a good explanation for the onset of complications such as hypoxia (due to ventilation-perfusion mismatch) and transient pulmonary hypertension [30]. According to the biochemical theory, fat globules migrating in capillary bed release free fatty acids and glycerol, which initiate an inflammatory response leading to altered microcirculation with increased vascular permeability, local ischemia, and hemorrhage [31, 32]. This theory may account for non-traumatic cases of FES, as well as the variable delay between fat release and onset of symptoms. Actually, the temporal presentation of symptoms has a bimodal distribution, with an early onset usually within 12 h and a late onset between 24 and 72 h after injury [5]. The same patient can experience relapsing symptoms after early-onset FES, as occurred in our patient #2, as well as in the case reported by Whalen et al. [16]

The presence of fat embolism is common in pediatric autoptic observations [6]; however, only a small number of patients admitted to PICUs/pediatric trauma centers after major trauma experiences the typical symptoms of post-traumatic FES, so that a description of the clinical course of these patients is limited to single case reports or as a part of larger series including mostly adult patients. The discrepancy between autoptic and clinical findings could be explained by the fact that the passage of fat globules into the systemic circulation, although frequent, does not usually produce clinical changes; moreover, the true incidence of post-traumatic FES could be underestimated in more severely injured children.

Although the criteria proposed by Gurd may help in diagnosis [8], FES often represents a major diagnostic challenge to most clinicians. Besides traditional clinical signs, cytological examination of broncho-alveolar lavage may be useful to strengthen the clinical suspect when the diagnosis is not clear [33, 34]. In addition, an elevated serum interleukin-6 level may be useful as an early marker of FES in patients with isolated skeletal trauma, combined to the commonly altered laboratory findings [35].

In our series, a femoral fracture was always present, whereas the time gap between the injury and the clinical syndrome was usually between 18 and 24 h. Neurological impairment was evidenced in five out of eight episodes, having a delayed recovery in two cases and an unfavorable neurological outcome for one of them: in these patients, brain magnetic resonance imaging (MRI) showed the typical "starfield" pattern determined by multiple ischemic foci, while brain CT scan remained persistently normal. Brain damage may progress to severe cerebral edema, leading to rapid deterioration and requiring a surgical treatment [11, 36]. The incidence of patent foramen ovale is known to be higher in younger people [37, 38]. This may allow larger fat globules to pass to the systemic circulation and potentially cause more frequent and/or severe neurologic symptoms in pediatric and adolescent patients. Brain involvement may worsen the prognosis of post-traumatic FES; clinical findings vary from confusion to encephalopathy with coma and seizures [39]: in our report, four out of seven patients sustained cerebral fat embolism, with typical CT or MRI findings. Transient deficits were observed, while long-term neurological impairment was less common.

The etiology of FES is likely secondary to a combination of the mechanical and biochemical pathways. The presence or the reopening of a patent foramen ovale with right-to-left shunt due to pulmonary hypertensionmay be associated with an increased risk for FES-related systemic manifestations, due to larger fat globules, though several studies failed to demonstrate any intracardiac shunts [40]. However, fat globules ranging from 7 to 10 μm in diameter have been documented to cross the pulmonary vasculature [41].

Respiratory distress has long been recognized as an essential feature of post-traumatic FES: pulmonary involvement can occur in up to 92–95% of cases, while hypoxemia is almost universally present. In our series, four out of seven patients developed a severe ARDS picture, while alveolar hemorrhage was evidenced in three patients. Hypoxemia can also be worsened by pleural effusions, lung contusion, and transfusion-related lung injury, all consistent with major trauma. Management of ARDS should follow current recommendations for ventilator setting, including low tidal volumes and individualized PEEP [42]. In case of refractory hypoxemia, several salvage strategies can be adopted. High-frequency oscillatory ventilation (HFOV) could be necessary, particularly when post-traumatic FES syndrome involves infants, as depicted in the case by Amigoni et al. [19]. Even inhaled nitric oxide represents a safe and feasible option in this condition, since it can improve the ventilation/perfusion mismatch by redistributing lung perfusion to well-aerated areas; moreover, it may offer a benefit for the prevention or treatment of pulmonary hypertension [43]. In patients with obstructive shock from massive pulmonary embolism, early introduction of vasoactive drugs is crucial; in this view, dobutamine is probably superior to norepinephrine in restoring right ventricle function [44]. While invasive ventilation is frequently needed due to both neurological impairment and associated chest injury, most authors agree on the clinical advantage of early weaning from invasive ventilation. Actually, in our series, four patients received NIV as a part of respiratory support. Tracheostomy is required in case of long-lasting neurological impairment.

To date, symptomatic and supportive therapy remains the main approach for post-traumatic FES, since a specific treatment has not been yet identified. Treatment of hypoxemia, adequate hemodynamic support a and prompt recognition of neurologic deterioration are fundamental therapeutic goals [5, 45]. Early immobilization, stabilization and fixation of long-bone fractures contribute to prevent the release of fat emboli [45, 46]. Systemic corticosteroids administration is suggested to be beneficial in preventing FES and hypoxia in patients with long-bone fractures, since these drugs can blunt the inflammatory response, although the quality of evidence is low [47–49]. The role of inhaled corticosteroids in the prophylaxis of post-traumatic FES is controversial [50, 51]. Statins may represent a promising treatment for fat embolism: their main effect lies in the reduction of cholesterol synthesis in the liver by inhibition of HMG-CoA reductase; however, statins have pleiotropic effects, including modulation of inflammatory response and improvement of endothelial function, which have been observed even in short therapeutic courses and which could account for a beneficial effect in the acute management of FES [52, 53]. Albumin has shown therapeutic effects in experimental models of FES, likely due to its ability to bind free fatty acids, which are largely involved in the inflammatory cascade ultimately leading to lung injury [54]; still, benefits associated with its use in clinical practice are uncertain. Heparin is known to stimulate lipase activity and improve clearance of lipids from the bloodstream, but it also causes an increase in free fatty acids which could worsen tissue injury [55]. Moreover, its use can be considered unsafe, since some cases of post-traumatic FES can be complicated by alveolar hemorrhage, as reported in our series.

Conclusion

Post-traumatic FES is a rare condition in pediatrics. The wide spectrum of clinical manifestations — as depicted in the present series — of this uncommon multi-faceted condition requires a high level of suspicion. A delay in diagnosis should be avoided, since the outcome of patients with post-traumatic FES who promptly receive appropriate supportive care is generally favorable. These patients should be managed in a tertiary referral center with the required expertise and high-volume flow of critically ill trauma patients.

Author contribution Marco Piastra conceived the study, collected, and interpreted the case series data and performed the statistical analysis. Enzo Picconi contributed to data collection, gave important contribute to paper preparation, and drafted the manuscript. Tony Christian Morena and Vittoria Ferrari were involved in manuscript preparation. Camilla Gelormini and Anselmo Caricato were responsible for patient care and contributed to data collection. Daniele De Luca, Federico Visconti, and Giorgio Conti contributed important intellectual content to the manuscript. All authors read and approved the final manuscript.

Data availability The data that support the findings of this study are available from the corresponding author, [EP], upon request.

Declarations

Ethics approval This study was approved by the institutional review board (Prot. 30870/19) on September 12, 2019, at Fondazione Policlinico Universitario "A. Gemelli" IRCCS – Rome, Italy.

Consent to participate Not applicable.

Competing interests The authors declare no competing interests.

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