Fat embolism

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Key points

Fat embolism syndrome is a clinical diagnosis with non-specific/insensitive diagnostic tests.

A high index of suspicion is important to ensure diagnosis.

The classic triad of respiratory changes, neurological abnormalities, and petechial rash is not always present.

Treatment is supportive.

Prophylactic steroid therapy may be considered for patients at a high risk.

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Although its original clinical description dates from 1873,[1] fat embolism syndrome remains a diagnostic challenge for clinicians. The term fat embolism indicates the often asymptomatic presence of fat globules in the lung parenchyma and peripheral circulation after long bone or other major trauma. The majority (95%) of cases occur after major trauma. Fat embolism syndrome is a serious consequence of fat emboli producing a distinct pattern of clinical symptoms and signs. It is most commonly associated with fractures of long bones and the pelvis, and is more frequent in closed, rather than open, fractures. The incidence increases with the number of fractures involved. Thus, patients with a single long bone fracture have a 1–3% chance of developing the syndrome, but it has been reported in up to 33% of patients with bilateral femoral fractures.[2] Fat embolism syndrome can also occur in relation to other trauma, for example, soft tissue injury, liposuction, bone marrow harvest (Table 1). Non-trauma-related causes (e.g. acute pancreatitis, sickling crisis) are less likely to lead to fat embolism syndrome compared with those associated with trauma. An overall mortality of 5–15% has been described.[3]

Clinical presentation

Fat embolism syndrome typically presents 24–72 h after the initial injury. Rarely, cases occur as early as 12 h or as much as 2 weeks later.[4] Patients present with a classic triad:

(i) respiratory changes;
(ii) neurological abnormalities;
(iii) petechial rash.

Respiratory changes are often the first clinical feature to present. Dyspnoea, tachypnoea, and hypoxaemia are the most frequent early findings. The severity of these symptoms varies but a number of cases may progress to respiratory failure and a syndrome indistinguishable from acute respiratory distress syndrome (ARDS) may develop. Approximately one-half of the patients with fat embolism syndrome caused by long bone fractures develop severe hypoxaemia and respiratory insufficiency and require mechanical ventilation.[5]

Neurological features resulting from cerebral embolism frequently present in the early stages. Cerebral emboli produce neurological signs in up to 86% of cases and often occur after the development of respiratory distress. The changes range across a wide spectrum from mild confusion and drowsiness through to severe seizures. The more common presentation is with an acute confusional state but focal neurological signs, including hemiplegia, aphasia, apraxia, visual field disturbances, and anisocoria, have been described. Seizures and decorticate posturing have also been seen. Fortunately, almost all neurological deficits are transient and fully reversible.

The characteristic *petechial rash* may be the last component of the triad to develop. It occurs in up to 60% of cases and is due to embolization of small dermal capillaries leading to extravasation of erythrocytes. This produces a petechial rash in the conjunctiva, oral mucous membrane, and skin folds of the upper body, especially the neck and axilla.[6] It does not appear to be associated with any abnormalities in platelet function. The rash appears within the first 36 h and is self-limiting, disappearing completely within 7 days.

A number of minor features of fat embolism syndrome may be present and these appear to result from the release of toxic mediators secondary either to the initial injury or to dysfunctional lipid metabolism. These include pyrexia, tachycardia, myocardial depression, ECG changes indicative of right heart strain, soft fluffy retinal exudates with macular oedema scotomata (Purtscher's retinopathy), coagulation abnormalities (which mimic disseminated intravascular coagulation),[7] and renal changes presenting as oliguria, lipiduria, proteinuria, or haematuria. The presence of any these features may be of help in diagnosis (discussed later).

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Table 1 Conditions associated with fat embolism

Trauma related
Long bone fractures
Pelvic fractures
Fractures of other marrow-containing bones
Orthopaedic procedures
Soft tissue injuries (e.g. chest compression with or without rib fractures)
Burns
Liposuction
Bone marrow harvesting and transplant
Non-trauma related
Pancreatitis
Diabetes mellitus
Osteomyelitis and panniculitis
Bone tumour lyses
Steroid therapy
Sickle cell haemoglobinopathies
Alcoholic (fatty) liver disease
Lipid fusion
Cyclosporine A solvent

Pathogenesis

The mechanism producing fat embolism syndrome is not clearly understood; mechanical and biochemical causes have been proposed. Fat emboli may occur either by direct entry of depot fat globules from disrupted adipose tissue or bone marrow into the bloodstream in areas of trauma (mechanical) or via production of toxic intermediaries of fat present in the plasma (biochemical). It is feasible that both mechanisms are involved, with embolized fat from traumatized tissues undergoing a subsequent biochemical degradation.

'Mechanical' fat embolism (mechanical theory)

The suggestion that fat from disrupted bone marrow or adipose tissue is forced into torn venules in areas of trauma originated in the early 20th century. Fractures of marrow-containing bone have the highest incidence of fat embolism syndrome and cause the largest volume fat emboli. This may be because the disrupted venules in the marrow remain tethered open by their osseous attachments. Therefore, the marrow contents may enter the venous circulation with relatively little difficulty.

This theory is supported by the description of 'echogenic material' passing into the right heart during orthopaedic surgery. Further emboli will produce an increase in pulmonary artery and right heart pressures, and material can pass through a patent foramen ovale into the systemic circulation, resulting in paradoxical embolism. Some studies have demonstrated the appearance of embolic material in the systemic circulation in the absence of a patent foramen ovale, potentially explaining neurological disease and petechiae on the basis of obstructive microembolism.[8] This would depend on the embolized fat being sufficiently deformable to be forced through the pulmonary capillaries by the raised right ventricular pressure.

However, this theory does not sufficiently explain the 24–72 h delay in development after the acute injury.

Production of toxic intermediaries (biochemical theory)

There are a number of biochemical mechanisms potentially involved in the development of fat embolism syndrome. The most widely held is that the embolized fat is degraded in plasma to free fatty acids. Although neutral fat, such as is found in bone marrow, does not cause an acute lung injury, it is hydrolysed over the course of hours to several products, including free fatty acids, which have been shown to cause ARDS in animal models. Free fatty acids have also been associated with cardiac contractile dysfunction, which can be a feature of fat embolism syndrome. The plasma lipase concentration is increased in some patients.

Serum from acutely ill patients has been shown to have the capacity to agglutinate chylomicrons, low-density lipoproteins, and liposomes of nutritional fat emulsions. C-reactive protein, which is elevated in these patients, appears to be responsible for lipid agglutination and may also participate in the mechanism of non-traumatic fat embolism syndrome.

The delay in development of symptoms could be explained by the timescale required to produce these toxic metabolites. The onset of symptoms may coincide with the agglutination and degradation of fat emboli. Levels of circulating free fatty acids are moderately elevated in fracture patients compared with controls. Nevertheless, evidence for these mechanisms of injury remains largely circumstantial.

Diagnosis

Diagnosis is usually made on the basis of clinical findings but biochemical changes may be of value. The most commonly used set of major and minor diagnostic criteria are those published by Gurd (Table 2). The major criteria are based on the classic triad and clinical diagnosis is made by the presence of respiratory insufficiency, neurological impairment, and a petechial rash. In the appropriate setting, the rash is considered pathognomonic, although it is present in only 20–50% of cases.[5] For the diagnosis of fat embolism syndrome, at least one major and four minor criteria must be present.

The reliability of these criteria have been questioned and other schemes based more on respiratory features alone (Table 3) have been proposed.[14] More recently, a fat embolism index has been proposed as a semi-quantitative means of diagnosing fat embolism syndrome, in which there are seven clinical features (Table 4); each one is given a particular score.[13] A score of >5 is required for a positive diagnosis.

An unexplained anaemia (70% of patients) and thrombocytopenia (platelet count $<150\ 000\ mm^{-3}$ in up to 50% of patients) are often found. Serum lipase concentration increases after bone injuries and is often misleading. Cytological examination of urine,

Table 2 Gurd's criteria

Major criteria
Axillary or subconjunctival petechiae
Hypoxaemia Pa_{O_2} <60 mm Hg; $F_{I_{O_2}} = 0.4$)
Central nervous system depression disproportionate to hypoxaemia
Pulmonary oedema
Minor criteria
Tachycardia <110 bpm
Pyrexia <38.5°C
Emboli present in the retina on fundoscopy
Fat present in urine
A sudden inexplicable drop in haematocrit or platelet values
Increasing ESR
Fat globules present in the sputum

blood, and sputum with Sudan or Oil Red O staining may detect fat globules that are either free or in macrophages. Blood lipid concentration is not helpful for diagnosis because circulating fat concentrations do not correlate with the severity of the syndrome. Hypocalcaemia, due to binding of the free fatty acids to calcium, and elevated serum lipase have also been reported.

A number of radiological findings have been described but none is diagnostic of fat embolism syndrome. The chest X-ray is often normal initially but in some patients bilateral fluffy shadows develop as respiratory insufficiency worsens. A minority has diffuse or patchy air space consolidation, due to oedema or alveolar haemorrhage; this is most prominent in the periphery and bases. Ventilation/perfusion scans may demonstrate a mottled pattern of sub-segmental perfusion defects with a normal ventilatory pattern.

Focal areas of ground glass opacification with interlobular septal thickening are generally seen on chest CT but ill-defined centrilobular and subpleural nodules representing alveolar oedema, microhaemorrhage, and inflammatory response secondary to ischaemia and cytotoxic emboli may be seen.[9] MRI of the brain may reveal high-intensity T2 signals; this correlates with the degree of neurological impairment found clinically.

It is a common misconception that the presence of fat globules, either in sputum, urine, or a wedged PA catheter, is necessary to confirm the diagnosis. However, the recovery of fat globules is of uncertain significance. In one study, the presence of fat was demonstrated in the serum of >50% of patients with fractures who had no symptoms suggestive of fat embolism syndrome.[10] The use of bronchoscopy with bronchoalveolar lavage to detect fat droplets in alveolar macrophages as a means to diagnose fat embolism has been described in trauma patients and patients with the acute chest syndrome of sickle cell disease. However, diagnostic criteria vary and the sensitivity and specificity are unknown.

Table 3 Lindeque's criteria

Sustained Pa_{O_2} <8 kPa
Sustained P_{CO_2} of >7.3 kPa or a pH <7.3
Sustained respiratory rate >35 breaths min^{-1}, despite sedation
Increased work of breathing: dyspnoea, accessory muscle use, tachycardia, and anxiety

Table 4 Schonfeld's criteria

Petechiae	5
Chest X-ray changes (diffuse alveolar infiltrates)	4
Hypoxaemia (Pa_{O_2} < 9.3 kPa)	3
Fever (>38°C)	1
Tachycardia (>120 beats min^{-1})	1
Tachypnoea (>30 bpm)	1
Cumulative score >5 required for diagnosis	

Treatment and prevention

There is no specific therapy for fat embolism syndrome; prevention, early diagnosis, and adequate symptomatic treatment are of paramount importance. Supportive care includes maintenance of adequate oxygenation and ventilation, stable haemodynamics, blood products as clinically indicated, hydration, prophylaxis of deep venous thrombosis and stress-related gastrointestinal bleeding, and nutrition. The goals of pharmacotherapy are to reduce morbidity and prevent complications. Supportive care is the mainstay of therapy for clinically apparent fat embolism syndrome. Mortality is estimated to be 5–15% overall, but most patients will recover fully.[2, 11]

Early immobilization of fractures reduces the incidence of fat embolism syndrome and the risk is further reduced by operative correction rather than conservative management. Another strategy to prevent fat embolism syndrome is to limit the elevation in intraosseous pressure during orthopaedic procedures, in order to reduce the intravasation of intramedullary fat and other debris.[14] In a randomised trial of 40 patients, half were randomised to receive a venting hole for drainage of the medullary cavity between the greater and the lesser trochanter in order to limit intraoperative rises in intraosseous pressure. Significantly fewer major embolic events were detected by transoesophageal echocardiography in the venting group (20% *vs* 85%). Other operative refinements may also serve to limit intraosseous pressure, including the use of cementless fixation of hip prostheses and unreamed intramedullary femoral shaft stabilization.[14]

The use of corticosteroid prophylaxis is controversial, largely because it is difficult to definitively prove efficacy in a condition with a low incidence, unclear risk factors, low mortality, and a good outcome with conservative management. Nevertheless, a number of studies report decreased incidence and severity of fat embolism syndrome when corticosteroids are given prophylactically.[12, 13] In a double-blind randomized study, 64 consecutive patients with lower-extremity long-bone fractures received either placebo or methylprednisolone, 7.5 mg kg^{-1} every 6 h for 12 doses.[13] Fat embolism syndrome was diagnosed in 9 of 41 placebo-treated patients and 0 of 21 steroid-treated patients ($P < 0.05$). No complications related to steroid treatment were observed.

One rational, conservative approach would be to give prophylactic steroid therapy only to those patients at high risk for fat embolism syndrome, for example, those with long bone or

pelvic fractures, especially closed fractures. Methylprednisolone 1.5 mg kg^{-1} i.v. can be administered every 8 h for six doses.

Corticosteroids have been extensively studied, and recommended by some, for the management of the fat embolism syndrome. The proposed mechanism of action is largely as an anti-inflammatory agent, reducing the perivascular haemorrhage and oedema. There are insufficient data to support initiating steroid therapy once fat embolism syndrome is established. An experimental study showed no beneficial effect, and there have been no prospective, randomized, and controlled clinical studies that have demonstrated a significant benefit with their use.

A prospective study of 58 patients with uncomplicated fractures showed that the treatment of patients with aspirin resulted in significant normalization of blood gases, coagulation proteins, and platelet numbers when compared with controls. Heparin is known to clear lipaemic serum by stimulating lipase activity and has been advocated for the treatment of fat embolism syndrome. However, activation of lipase is potentially dangerous if increases in free fatty acids are an important part of the pathogenesis. There is also a possibility of increased risk of bleeding in patients with multiple trauma.

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