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Possible role of short-term parenteral nutrition with fat emulsions for development of haemophagocytosis with multiple organ failure in a patient with traumatic brain injury

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Abstract. We describe a case of life-threatening haemophagocytosis after a short term nutrition with fat emulsion in a 21-year-old woman who sustained an isolated traumatic brain injury. Hypertriglyceridemia and "creaming plasma" were observed after a three-day period of parenteral fat nutrition (Intralipid 20%). She also developed rash, high fever (40–41 °C), hypertension, raised intracranial pressure, hepatic and renal failure, haemolysis, marked thrombocyto- and leucopenia, coagulation disorder and pulmonary failure. These symptoms, together with a typical bone marrow smear, indicated haemophagocytosis with hyperactivation of the monocyte-macrophage system. We suggest that the hyperactivation was an effect of fat retention or agglutination of the fat particles; the initial triggering mechnism may emanate from the brain damage by hypercytokinaemia. The steroid treatment given most likely contributed to the successful outcome, as indicated by the stepwise improvement related in time to the steroid infusions.

Key words: Haemophagocytosis – Hyperlipidaemia – Multiple organ failure – Intravenous fat emulsions – Brain injury – Cytokines

Phagocytosis by macrophages is a normal mechanism for clearance of particulate agents such as bacteria and viruses from blood, but also for elimination of erythrocytes which have served their time. During excessive macrophage activation, all types of blood cells can be uncontrollably cleared by this system, a process denoted haemophagocytosis [1, 2]. This syndrome has been described after long term (>3 months) parenteral treatment with fat emulsions in children [3], in a histiocyte syndrome called familial haemophagocytic lymphohistiocytosis (FHL) [1, 2, 4], during severe infections [5] and after i.v. administration of iodinated lipid emulsions used as contrast media for radiographic examination of the liver and spleen [6]. Haemophagocytosis is associated with fever, rash, anaemia, thrombocyto- and leucopenia, coagulation disorders and sometimes multiple organ failure.

An increased release of cytokines is suggested to be involved in the pathogenesis of these clinical syndromes, and steroid treatment is beneficial [1–6].

The present report describes a case of haemophagocytosis of a non-typical genesis as developed after a short-term infusion of fat emulsions in a patient with traumatic brain injury.

Case history

This previously healthy 21-year-old woman sustained from an isolated brain injury in a traffic accident. She underwent surgery for a subdural and an epidural haematoma and was equipped with an intraventricular catheter for intracranial pressure measurement shortly after arrival at the hospital. The CT-scan indicated marked brain oedema. The initially high ICP around 45 mmHg was reduced to levels below 20 mmHg during the first two days by the standard pharmacological brain oedema treatment used in our ICU (thiopental, metoprolol, clonidine and dihydroergotamine) [7, 8]. The patient's circulation was initially stable.

A fat emulsion (Intralipid 20%) and amino acids (Vamin 14) were added to the parenteral glucose nutrition at day 3 after the accident. Plasma was visibly normal after centrifugation, and S-Triglycerides showed normal values. Four days after the accident, when Intralipid had been given for 2 days (500ml+500ml), blood pressure increased to systolic values above 170 mmHg in spite of aggressive antihypertensive treatment with metoprolol and clonidine. Body temperature increased to 40 °C (Fig. 1e). By 10 h later, ICP started to rise slowly from normal values (<10 mmHg). On day 5, when ICP had increased to about 50 mmHg, a partial left temporal lobe resection was performed acutely to prevent herniation of the brain. On day 7, an extremely viscous and white turbid plasma was observed and S-Triglycerides were high (8.5 mmol/l), while S-Cholesterol (2.6 mmol/l), HDL-cholesterol (0.41 mmol/l) and LDL-cholesterol (1.1 mmol/l) were low. At that time the patient had been given a total of 1500 ml of Intralipid. Blood (2000 ml) was removed by acute venesection as "partial plasmapheresis" and compensated for by transfusions of blood and fresh frozen plasma. The patient initially showed a state of compromised peripheral circulation (hypodynamic circulation) which now turned into peripheral hyperaemia (hyperdynamic circulation). However, body temperature was still 40–41 °C (Fig. 1e). Concentration of C-reactive protein (CRP) increased and reached its highest value on day 7 (when the "creaming" plasma was first ovserved) (Fig. 1e), rapidly followed by signs of multi-

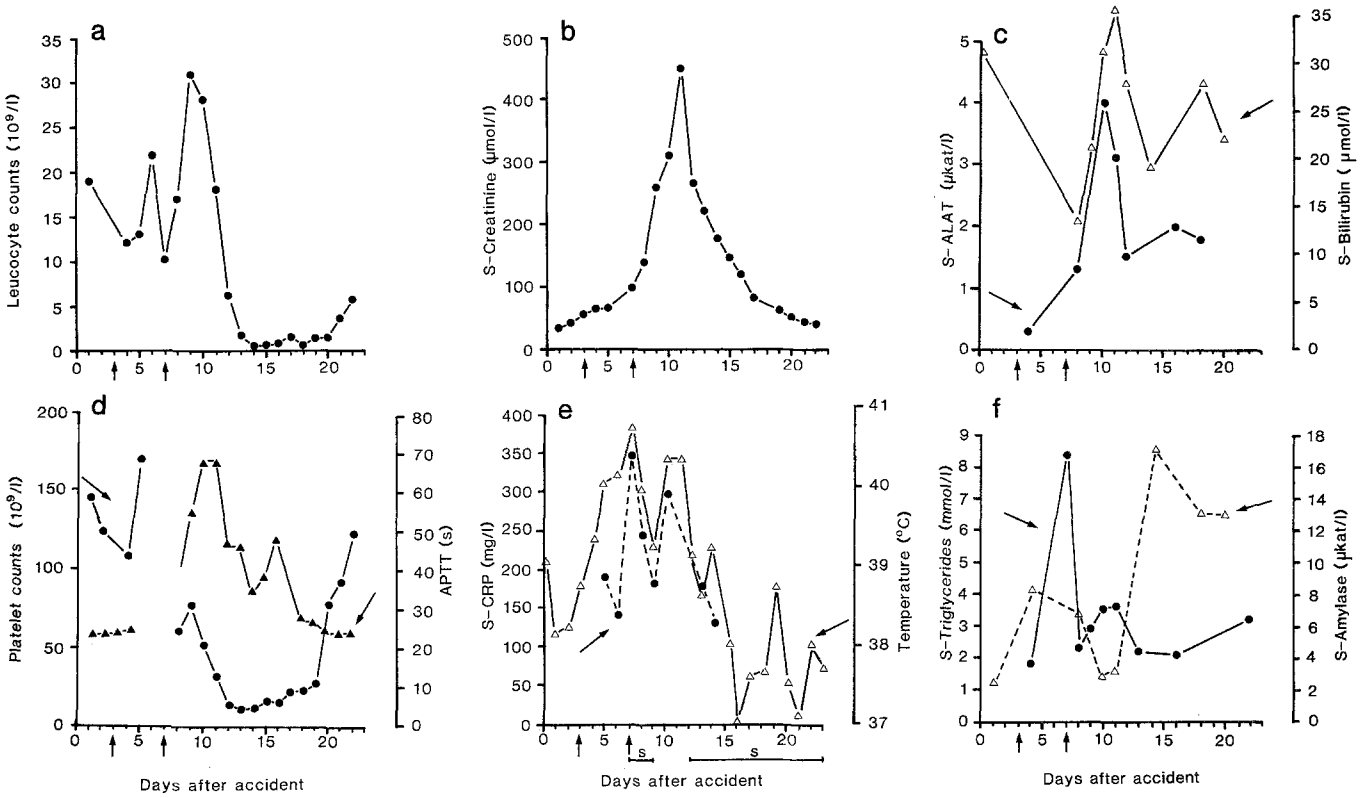

Fig. 1. Variation in **a)** leucocyte counts, **b)** S-Creatinine, **c)** S-ALAT ●———● and S-Bilirubin △———△, **d)** platelet counts ●———● and APTT ▲———▲, **e)** S-CRP ● – – – ● and maximum temperature △———△, and **f)** S-Triglycerides ●———● and S-Amylase △ – – – △ during the first 23 days following the accident. The first *arrow* at the abscissa indicates start of parenteral fat nutrition on day 3 and the second *arrow* "creaming" of plasma and termination of parenteral fat nutrition on day 7. S in e) indicates days with steroid therapy

ple organ failure. Thus, S-Creatinine, Alanine amino transferase activity, S-Amylase and leucocyte count increased while platelet count decreased (Fig. 1). Increase in S-Amylase is a finding quite often observed after a head trauma in our ICU. Oxygenation was impaired, and coagulopathia developed as evidenced by minor bronchial bleedings, haematuria and low levels of antithrombin III (35%), the latter normalized with substitution (>90%).

Later, platelet and leucocyte counts decreased markedly (Fig. 1 a, d) to values below 10×10^9/l and 1.0×10^9/l respectively. Platelets were substituted with restriction and a total of 14 units of platelet concentrate were given. Haemoglobin concentration decreased significantly and there was a need for transfusion of 500 ml blood/day although no significant bleedings were observed, indicating haemolysis. Haemolysis may also explain the increase in S-Bilirubin (Fig. 1 c). Bone marrow smear showed plenty of normal megakaryocytes. The sample was very rich in macrophages containing debris, erythrocytes and sometimes granulocytes, all together indicating haemophagocytosis. Besides a limited period of time when the patient was given ciprofloxacin and vancomycin, cefuroxime was the only antibiotic treatment given. Bacteriological investigations of blood, urine, bronchial secretion and liquor were all negative, also in the antibiotic-free period of five days from day nine. Sukralfat was used as ulcus prophylaxis except days 3–5 when ranitidine was given. Morphine, fentanyl and midazolam were used as sedatives and analgetics.

Blood glucose levels were kept below 7 g/l with extra insulin. Although intravenous fat substitution was discontinued, S-Triglycerides remained elevated during the following weeks (Fig. 1 f).

After the temporal lobe resection, ICP never exceeded 15 mmHg. Steroid therapy in terms of methylprednisolone was first given for 2 days starting day 7 (1 g/day). It was followed by rapid clinical improvement. However, after the 2 followed by rapid clinical improvement. However, after the 2 following days without steroids, CRP and temperature started to rise again (Fig. 1 e). Therefore, the steroid treatment was reintroduced after another day to be continued of a successively reduced dose for two weeks.

Six months after the accident, the patient was well recovered with only minor neurological sequeela.

Discussion

This paper describes a syndrome, the main features of which were hyperlipidaemia and multiple organ failure in combination with haemophagocytosis which developed in a previously healthy patient suffering from a severe traumatic brain injury. A possible pathogenic interpretation of the clinical course will be given below. The main principles are illustrated in Fig. 2.

The marked hyperlipidaemia shows that the capacity of lipoprotein lipase (LPL) to eliminate fat from the circulation was insufficient. Most likely, this was caused by a markedly reduced enzyme activity as only small amounts of fat were given. Besides long-term heparin treatment, catecholamines and cytokines are known to impair LPL activity [9, 10]. As no heparin was given, the low LPL activity most likely can be ascribed to catecholamines and/or cytokine release. Catecholamines alone inhibit LPL in fat tissue but, if anything, they stimulate the LPL in heart and skeletal muscle [9]. Therefore, cytokines seem to be the main cause of the suppressed LPL activity. Also the clinical symptoms, often related to sepsis, like fever, hyper- and hypo-dynamic circulation etc., are com-

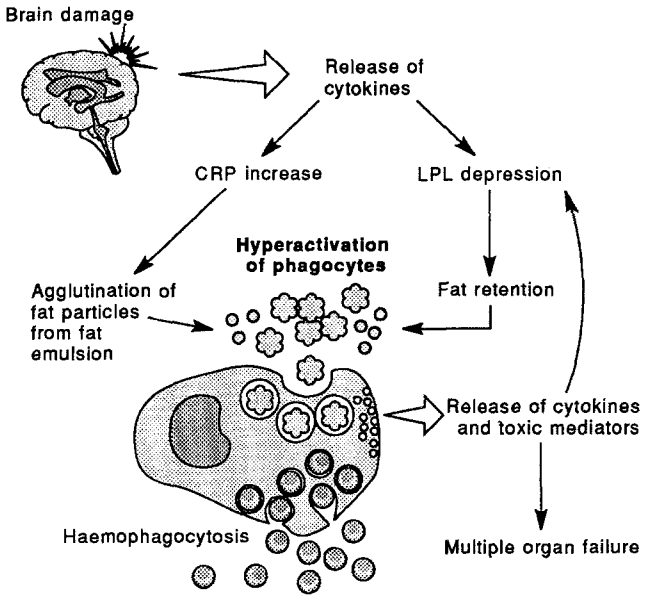

Fig. 2. A schematic overview of the proposed pathogenesis of fat emulsion-induced haemophagocytosis

patible with an excess release of cytokines [11]. Obviously the LPL activity continued to be inadequate for a long time after termination of the intravenous fat administration as the triglyceride concentration in plasma was high for weeks thereafter.

The clinical course and the bone marrow smear strongly indicated macrophage hyperactivation with phagocytosis not only of fat particles, but also of normal blood cells. Macrophage activation with haemophagocytosis is associated with the release of cytokines [3, 4, 12]. The time lag between the first symptoms (fever, hypertension) and the development of hyperlipidaemia is compatible with a causal relationship in time between an early cytokine release and a later impairment of the lipid removal process. The latter is in agreement with an assumption that the available clearing capacity of the reticuloendothelial system (RES) is fully utilized after some time of maximal activity; in addition, LPL activity is impaired [13]. Still, there must be another initial triggering mechanism for the macrophage activation and/or for the suppression of the LPL activity. Such mechanisms may be related to the release of substances from the damaged brain. It is known that cytokines like interleukines are released from the brain after a brain injury [14, 15]. Such substances depress LPL activity directly, leading to fat retention which may induce macrophage hyperactivation. Alternatively, substances from the damaged brain may trigger macrophage activation and release of further cytokines, thereby indirectly suppressing the LPL activity. It has also been shown that sera with high levels of CRP can, perhaps via opsonisation, trigger agglutination ("creaming") of fat particles (Intralipid) in vitro [16]. This could be the case in our patient, who had excessively high CRP values and "creaming" plasma. It is resonable to believe that during clearance from the blood of such large fat complexes the macrophage system will be hyperactivated, in analogy to what has previously been described after long-term parenteral treatment with fat in children [3, 12, 17]. The use of iodinated lipid emulsions as a macrophage imaging agent for X-ray investigation of the liver and the spleen [6] also exemplifies a situation with macrophage activation, causing adverse clinical symptoms similar to those seen in our patient.

As well as the criteria for haemophagocytosis, which include haemolysis, thrombocyto- and leucocytopenia, hypertension and a typical bone marrow smear, all the other symptoms such as high fever, rash, hypo and hyperdynamic circulation and multiple organ failure are also associated with syndromes which are related to the release of cytokines. This constellation of symptoms is perhaps best illustrated by a sepsis situation [11]. It is unlikely that any other drug given could be responible for the observed symptoms, not even ranitidine as it was given for only a short period of time.

The interplay in time between temperature, CRP on the one hand and the steroid therapy on the other, supports the opinion that the observed improvements were caused by the steroid therapy rather than by discontinuation of fat nutrition and were most likely due to depressed release of cytokines (Fig. 1e). Also in other types of haemophagocytosis, beneficial effects of steroids have been reported [3, 4]. Therefore, we believe that steroids should be included in the treatment if signs of haemophagocytosis and fat retention appear. The future may show if parenteral fat nutrition should be avoided in patients with acute brain damage as indicated by this study. We believe that parenteral fat emulsions should be used with restriction at high CRP values, perhaps not only after a head trauma, but also in other severe conditions like sepsis, as a high CRP value per se reflects high levels of cytokines and thus low LPL activity [11]. The CRP value may be a predictor for the capacity of the body both to utilize and tolerate parenteral fat emulsions [9, 11]. A CRP value of 50–100 mg/l (above which creaming is described) could be an upper limit to use for these considerations [16]. Frequent control of the CRP level therefore might be a useful complement as a tool for monitoring of macrophage activity and tolerance of parenteral fat emulsions.

This case indicates that parenteral nutrition with only quite small amounts of fat emulsions under specific circumstances can initiate macrophage activation. It is possible that infusion of fat by administration of other fat containing drugs like long-term treatment with propofol in critically ill patients can also trigger these reactions.

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