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REVIEW

Bone marrow necrosis and fat embolism syndrome in sickle cell disease: Increased susceptibility of patients with non-SS genotypes and a possible association with human parvovirus B19 infection

Dimitris A. Tsitsikas [a,*], Giorgio Gallinella [b], Sneha Patel [a], Henry Seligman [a], Paul Greaves [a], Roger J. Amos [a]

[a] Department of Haematology, Homerton University Hospital NHS Foundation Trust, London, UK
[b] Department of Pharmacy and Biotechnology, University of Bologna, S. Orsola-Malpighi Hospital — Microbiology, Bologna, Italy

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ABSTRACT

Fat embolism syndrome (FES) due to extensive bone marrow necrosis (BMN) in sickle cell disease (SCD) is a potentially under-diagnosed complication associated with severe morbidity and mortality. We identified 58 cases reported in the world literature to date. Typically, patients presented with a seemingly uncomplicated vaso-occlusive crisis (VOC) and subsequently deteriorated rapidly with a drop in their haemoglobin and platelets, development of respiratory failure, encephalopathy and varying degrees of involvement of other systems. Overall mortality in the reported cases was 64% but differed according to the use of transfusion and was 29%, 61% and 91% for patients receiving exchange, top-up or no transfusion respectively. Patients most at risk appear to be those with a "milder" form of SCD as 81% of patients had a genotype other than HbSS and the majority had no history of significant sickle-related complications. Human parvovirus B19 (HPV B19) infection was documented in 24% of cases.

1. Introduction

Fat embolism syndrome (FES) results from the release of fat globules into the venous circulation and is associated with distinct clinical features comprising respiratory, neurological, cutaneous and haematological manifestations [1]. It is a complication mostly described in the context of long bone fractures or orthopaedic surgery; non-traumatic FES is very rare and is attributed to bone marrow necrosis (BMN) [2].

BMN refers to necrosis of myeloid tissue and medullary stroma in large areas of the haemopoietic bone marrow. Extensive BMN is associated with the development of pancytopenia with a leucoerythroblastic peripheral blood smear; characteristically, a striking number of circulating nucleated red blood cells (NRBCs) have been described. The bone marrow trephine shows disruption of normal marrow architecture with loss of fat spaces but generally preservation of the spicular architecture [3]. Up to 90% of cases of BMN occur in the context of cancer, most often haematological malignancy. Much rarer causes of BMN include autoimmune conditions, infections and sickle cell disease (SCD) [4]. Failure of the marrow microcirculation has been thought to be the common underlying feature [5].

FES due to extensive BMN was first described in 1941 in a woman with previously undiagnosed SCD who presented with pain, deteriorated rapidly and died [6]. Several case reports and small case series involving patients with SCD have been published since. The largest review to date from 2005, identified 24 cases in the literature. One third of those patients had HbSS and the remainder were associated with other genotypes, mostly HbSC. In one third of cases the diagnosis of SCD was not made until autopsy. A quarter presented comatose, all of whom had HbSC or HbSβ-thalassaemia. Nearly half of the female patients were pregnant [7].

In light of the limited published literature on this rare but often fatal syndrome, we undertook the present review to make as complete as possible a list of all reported cases to date, to describe clinical presentations and outcomes, to explore potential links with specific characteristics of SCD and to identify potential triggering factors.

2. Methodology

The following electronic databases were searched: Medline, Embase and CINAHL. The search terms were grouped and combined and included terms related to: 1) fat embolism (including systemic fat embolism, fat embolism syndrome), 2) bone marrow necrosis and 3) sickle cell (including sickle cell anaemia, disease, haemoglobin SC disease, sickle beta thalassaemia, drepanocytosis). Thesaurus terms were combined with text words on an 'OR' operator wherever available and appropriate. The search was not limited to a time frame or the English language.

This search strategy identified 228 articles of which 26 were duplicates. The title and abstracts of the remaining 202 were screened for eligibility according to the inclusion/exclusion criteria below. All of these articles were screened independently by three of the authors

* Corresponding author at: Homerton University Hospital NHS Foundation Trust, Department of Haematology, Homerton Row, London E96SR, UK. Tel.: +44 2085105021.
E-mail address: dimitris.tsitsikas@homerton.nhs.uk (D.A. Tsitsikas).

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(DT, SP and HS) and for an article to be rejected without reviewing the full text, all three had to agree. When it was not possible to ascertain eligibility from the title/abstract alone, the full text version was retrieved. All case reports were selected. Similarly, all papers where the title or the abstract indicated that a case was described were selected. Review papers were also selected in order to check their reference lists and identify more cases. Papers were excluded if there was no evidence of sickle cell disease or if there was only limited BMN and no evidence of fat embolism syndrome. Papers that described cases meeting our definition criteria for FES but were reported with a different diagnosis (e.g multi-organ failure syndrome), were also excluded.

93 papers were selected for inclusion and the full text version was accessed. The screening of reference lists identified a further 17 studies for extraction. All selected papers were then searched to check for other relevant papers that had cited them but no new papers were identified (Fig. 1). 11 authors were contacted to enquire further on sickle cell characteristics and evidence of HPV B19 infection for the patients they reported; we received 3 responses.

2.1. Definitions

FES was defined as multi- or single organ histologically proven involvement by fat and/or necrotic marrow emboli or development of acute respiratory distress and neurological manifestations or multiorgan failure with evidence of BMN (pathological proof or laboratory evidence). BMN was defined as histologically proven (autopsy or biopsy) extensive BMN or a relevant clinico-pathological picture in the context of FES; that is the rapid development of anaemia and thrombocytopenia with a leucoerythroblastic peripheral smear with high numbers of circulating NRBCs. BMN was accepted to be "extensive" if that was how it was characterized by the author of the report. If the genotype for a particular case was not given but was referred to as "sickle cell anaemia" it was presumed to be HbSS.

58 cases fulfilling the above criteria for BMN and FES were identified (Table 1). Data on cases of extensive BMN with no FES were also collected but classified separately. 16 such cases were identified (Table 2).

3. Limitations

This is a literature review of cases of BMN/FES in SCD published over a period spanning more than seventy years and as such has many limitations. It takes into account only published cases and relies mostly on the individual authors' interpretation of findings. Some of the cases are reported before the development of sophisticated diagnostic modalities such as MRI, before the description of the role of HPV B19 in SCD or even before the characterisation of some of the haemoglobin variants. As severe complications are not uncommon in patients with HbSS disease, such cases may have been under-reported introducing publication bias in our analysis. At the same time, patients with non-SS genotypes may also be under-reported; we find a large number of cases where SCD was only diagnosed at autopsy after developing FES with a fatal outcome. Patients with previously undiagnosed SCD who retain their spleen, such as those with non-SS genotypes, may not be recognised as such by pathologists and therefore not reported [8].

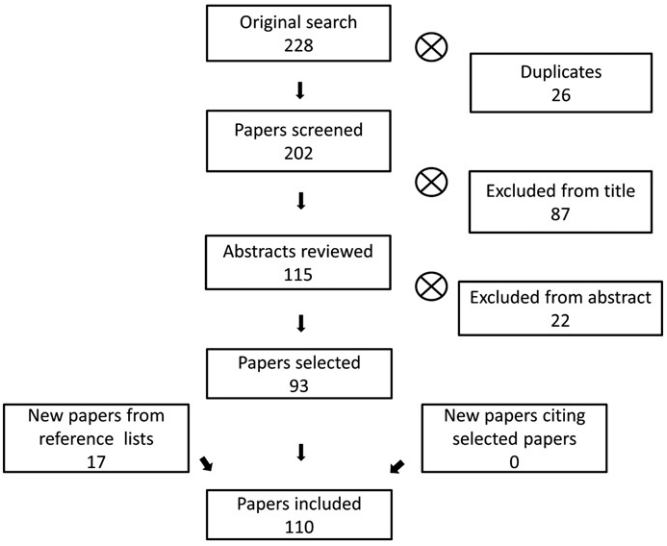

Fig. 1. Selection process.

4. Diagnosis and clinical features

BMN/FES was diagnosed at autopsy in 33 cases (57%). In an additional 10 cases (17%) there was histological confirmation of BMN from bone marrow trephine biopsy whereas the diagnosis in the rest of the cases was based on imaging, clinical presentation and laboratory features. The age of the patients ranged from 7 to 60 years (median 27). In 5 cases the age was not given. 7 patients (12%) were below the age of 16. 25 patients (43%) were male and 32 female (55%) (one not specified). Pain of unusual severity was the cardinal presenting symptom in all cases. Typically, patients presented with a seemingly uncomplicated VOC of unusual severity and fever and then deteriorated suddenly, usually within the space of few hours, with respiratory distress, altered mental status ranging from confusion to coma, a significant drop in the haemoglobin and platelets and varying degrees of involvement of other organs and systems (Fig. 2). Liver dysfunction occurring in 29% of cases was in the form of transient but often severe transaminitis. Lactic dehydrogenase (LDH) levels were provided in some reports and those were grossly elevated; always at least five times the upper normal limit and often in the several thousands U/l. Even though renal dysfunction or failure were documented in only 23% of cases, the kidneys were the second, after the lungs, most commonly affected organ by fat emboli at autopsy.

5. Risk according to genotype

11 patients (19%) had HbSS, 25 HbSC (43%), 10 HbSβ+ (17%), 2 HbSβ unspecified (3%), 2 HbSE (3%), 4 were classified as "non-SS" (7%) as the genotype was not given but from the age and clinical and/or haematological findings it was thought that it was extremely unlikely to represent homozygous SS patients and 4 are unknown (7%) (Fig. 3).

A number of previous publications have identified patients with HbSC most at risk of developing BMN/FES based on a small number of cases. The main hypothesis put forward to explain this association was the higher haematocrit in HbSC compared to that of HbSS patients and the resulting higher blood viscosity [9–13]. We confirm these previous observations and extend them to other non-SS genotypes that like HbSC are expected to confer a milder phenotype compared to SS homozygosity. In other words, when we look at the whole picture, it is not HbSC patients who have a particularly "high risk" for developing BMN/FES; it is HbSS patients who have a surprisingly "low risk".

6. Risk according to previous disease

Lack of serious previous complications from SCD was evident for the majority of cases where information about the disease was provided. 19 (33%) cases were previously undiagnosed and SCD was only found after the development of BMN/FES, often (13 cases) at autopsy. A mild course of SCD was documented in an additional 14 (24%) cases. In 19 (33%) cases no information about the previous course of SCD was provided. From the remaining 6 cases, 4 were reported to have suffered recurrent painful crises, 1 had a history of pneumonia and recurrent urinary tract infections and 1 of retinopathy. There was no case with documented previous stroke, renal failure or acute chest syndrome (ACS).