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# Reactive haemophagocytic syndrome in children with inflammatory disorders. A retrospective study of 24 patients

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## Abstract

*Background*. The reactive haemophagocytic syndrome (RHS) is a little-known life-threatening complication of rheumatic diseases in children. It reflects the extreme vulnerability of these patients, especially those with systemic-onset juvenile chronic arthritis (JCA). This immunohaematological process may be triggered by events such as herpes virus infection and non-steroidal anti-inflammatory drug therapy. Treatment has not been standardized.

*Methods*. We characterized this unusual disorder and determined its incidence by carrying out a retrospective study of patients identified over a 10-yr period in French paediatric units.

*Results*. Twenty-four cases (nine males, 15 females) were studied. Eighteen had typical systemic-onset JCA, two had polyarthritis, two had lupus and two had unclassifiable disorders. Clinical features at diagnosis included high spiking fever (24 patients), enlargement of the liver and spleen (14), haemorrhagic diathesis (six), pulmonary involvement (12) and neurological abnormalities (coma or seizures) (12). RHS was the first manifestation of systemic disease in three cases. Admission to intensive care was required in ten cases. Hypofibrinogenaemia, elevated liver enzymes and hypertriglyceridaemia were found consistently. Phagocytic histiocytes were found in 14 of 17 bone marrow smears. RHS was presumed to have been precipitated by infection in 11 cases (four Epstein–Barr virus, three varicella-zoster virus, one parvovirus B19, one Coxsackie virus, one *Salmonella*, one *Pneumocystis carinii*) and by the introduction of medication in three cases (Salazopyrin plus methotrexate; morniflumate; aspirin). Macrophage activation was indicated by high levels of monokines in the serum of two patients. Twenty patients had only one episode, three had an early relapse and one patient had two relapses. The treatment regimen was tailored to each child as the clinical course was variable. There was no response to intravenous immunoglobulins, which were used in four cases. Intravenous steroids at doses ranging from conventional to pulse methylprednisolone induced remission in 15 of 21 episodes when used alone as the first-line treatment. Cyclosporin A was consistently and rapidly effective, both when used as second-line therapy in all seven of the episodes in which steroids failed and in all five patients who received it as their first-line treatment. This supports a central role of T lymphocytes in the haemophagocytic syndrome. Two patients died. One patient with lupus died of congestive fulminant heart failure after 4 days, despite treatment with intravenous steroids and immunoglobulins, and one patient with systemic-onset JCA died from multiorgan failure despite aggressive therapy with pulsed steroids and etoposide.

*Conclusions*. RHS may be a more common complication of systemic disease in childhood than previously thought. This life-threatening complication should be diagnosed promptly, as it

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calls for the immediate withdrawal of potentially triggering medications, anti-infective therapy when relevant, and urgent immunosuppressive treatment, measures that are very often effective. Cyclosporin A may be the drug of choice.

KEY WORDS: Reactive haemophagocytic syndrome, Children, Cyclosporin A, Systemic-onset, juvenile chronic arthritis.

Reactive haemophagocytic syndromes (RHS) are characterized by the activation and uncontrolled non-malignant proliferation of T lymphocytes and macrophages, leading to the overproduction of cytokines, which accounts for the main clinical features. Patients usually present with an acute febrile illness, fulminant pancytopenia and hepatosplenomegaly, which makes it difficult to differentiate the condition from severe sepsis. Haemopoietic cells are actively ingested by monocytes/macrophages in various organs, including the lymph nodes, bone marrow, liver and spleen. This puzzling disorder of the reticuloendothelial system is currently classified among the reactional histiocytoses [1, 2]. It reflects an inappropriate immune response of the host. It is triggered by various events and is encountered in a variety of paediatric settings, the most common of which are familial erythrophagocytic lymphohistiocytosis [3] and viral infections, especially in immunocompromised children [4]. We reviewed the medical records of 24 children with RHS associated with inflammatory disease in France during the past 10 yr. This is the largest paediatric series of the syndrome reported to date. We discuss the clinical and biological findings and the treatment.

## Methods and results

### *Patients*

All paediatric units in France were surveyed for cases of RHS in patients with systemic disease. All the centres replied to our questionnaire. The case notes of 23 patients (plus one case from Zurich, Switzerland) treated at eight different pediatric units between 1987 and 1997 were studied (Table 1). We considered that these 24 cases constituted all the known cases during this period. The history, physical findings and laboratory results were recorded. Data collected included age at onset, sex and underlying medical conditions. Laboratory results analysed here include full blood count, prothrombin time, activated prothromboplastin time, thrombin time, fibrinogen, triglycerides, and cerebrospinal fluid and bone marrow studies when available. Treatment is described. Five of the children have been described briefly elsewhere [5].

TABLE 1. Clinical data at diagnosis in the 24 patients

| | No. of patients | % |
|---|---|---|
| Fever >39° | 24 | 100 |
| Liver enlargement | 14 | 58 |
| Spleen enlargement | 24 | 100 |
| Lymphadenopathy | 8 | 33 |
| Pulmonary involvement | 12 | 50 |
| Lethargy | 12 | 50 |
| ICU admission | 10 | 42 |
| Cardiac involvement | 10 | 42 |
| Renal involvement | 4 | 16 |
| Paradoxical improvement of the underlying disease | 3 | 12 |

The study group was composed of nine boys and 15 girls, whose ages ranged from 1 to 18 yr (median 10 yr). The diagnostic criteria for RHS were present in every patient, namely fever, splenomegaly, hypofibrinogenaemia, hypertriglyceridaemia and thrombocytopenia. At the time of admission, a diagnosis of systemic lupus erythematosus (SLE) was made in two patients who met the 1982 American Rheumatism Association criteria, with increased levels of anti-DNA antibody and low levels of complement (data not shown). Eighteen cases of systemic-onset juvenile chronic arthritis (SOJCA) were identified by the use of the criteria of the European League Against Rheumatism [6]. Two boys had distinct rheumatic disorders not yet included in the standard classifications of childhood rheumatic diseases. One of these boys, aged 16 yr, had polycyclic systemic disease characterized by recurrent sudden rises in temperature, myalgia, night sweats, eruptions and deteriorating general condition; the other had urticaria, fever, polyarthritis and pain. Two patients had polyarticular-onset juvenile chronic arthritis (JCA).

### *Clinical findings*

The RHS occurred a median of 1 yr after onset of the underlying disease (range 0–14 yr, mean 3.7 yr). It was the first manifestation of the underlying disease in three cases (one case of SLE and two cases of SOJCA). Four patients were in remission from the underlying disease at the onset of RHS and the remainder were in an active phase.

The clinical manifestations of RHS at presentation were similar in all the patients (Table 2) and included the sudden onset of non-remitting high fever with lethargy and hepatosplenomegaly in most cases. All the patients were acutely ill, RHS mimicking severe sepsis or a flare-up of the underlying disease. However, the pattern of non-remitting fever was different from that seen in SOJCA. Three patients showed a paradoxical improvement in the underlying inflammatory disease at the onset of RHS (i.e. disappearance of joint pain, signs and symptoms of arthritis, and normalization of the erythrocyte sedimentation rate).

Three children had renal involvement. Patient 1 was admitted at age 11 yr for fever, fatigue, facial rash

TABLE 2. Possible trigger in 14 of the 24 patients

| Trigger | No. of patients |
|---|---|
| Infections | |
| EBV | 4 |
| VZV | 3 |
| Coxsackie virus B1 | 1 |
| *Salmonella enteritidis* | 1 |
| *Pneumocystis carinii* | 1 |
| Parvovirus B19 | 1 |
| Medications | |
| Morniflumate (+ibuprofen?) | 1 |
| Sulphasalazine 50 mg/kg/day + MTX 0.3 mg/kg/week | 1 |
| Aspirin | 1 |
| Total | 14 |

and polyadenopathy. She developed acute respiratory distress but bronchoalveolar lavage was negative. Numerous examples of haemophagocytosis were found in the lymph nodes and bone marrow. Her condition worsened and she was admitted to the intensive care unit (ICU) because of renal impairment (maximum creatinaemia 350 $\mu$mol/l) and heart failure, acute respiratory distress and lethargy. The course was promptly reversed by intravenous (i.v.) steroid treatment. A diagnosis of lupus was suggested by antinuclear antibody positivity and a positive Coombs test. She subsequently developed marked proliferative glomerulonephritis 2 yr after this episode. The child was well on low-dose steroids at follow-up 11 yr later. The inappropriate macrophage activation syndrome had not recurred.

Patient 2 was on ibuprofen for SOJCA. A urinary tract infection was diagnosed. Morniflumate suppositories were prescribed. She was subsequently admitted to the ICU for seizures, coma (Glasgow scale $<5$), haemorrhagic diathesis and anuria (serum creatinine 500 $\mu$mol/l, lactic acidaemia 5.2 mmol/l). She was intubated. Physical examination revealed marked cervical lymphadenopathies, splenic enlargement and mild hepatomegaly. Haemophagocytosis was present on bone marrow smears. The cerebrospinal fluid (CSF) was hypercellular. Three infusions of methylprednisolone 300 mg/m$^2$/day induced full clinical remission. The anuria resolved promptly and she regained consciousness. She is doing well, and has not relapsed. The disease was moderately active 7 yr later.

Patient 3 had had severe SOJCA from 4 yr of age, with numerous flare-ups. She died at age 7 of fulminant RHS with oliguria and a nephrotic syndrome, despite a transient improvement on pulsed steroids and etoposide. Coxsackie B1 infection might have been involved.

Ten patients had cardiac involvement (dilated cardiomyopathy identified by ultrasound examination). Because of congestive heart failure and haemodynamic instability, three of these 10 patients required admission to the ICU and treatment with inotropic agents. The cardiopathy resolved rapidly on steroid treatment (in less than 10 days, on average), except in two patients, one of whom had acute haemophagocytic lupus (see above). Pericardial effusion was also present in five patients. An episode of supraventricular tachycardia occurred in one case.

Four patients had a haemorrhagic syndrome, two with extensive purpura and bruising, one with gastrointestinal haemorrhage and one with gross epistaxis.

Ten patients were acutely ill and required ICU admission. Eight patients required mechanical ventilation for respiratory and/or heart failure, or coma.

Sixteen patients had dysfunction of the central nervous system (CNS) [coma (Glasgow scale $<5$) in three; irritability, disorientation and a vacant stare with extreme fatigue in six; headache in three; papilloedema in three; and seizures in one]. Cranial CT scan was normal in the five cases in which it was done.

A precipitating factor was suspected in 14 of the 31 episodes (Table 2). These factors included primary Epstein–Barr virus (EBV) infection with a typical humoral immune response, including IgM antibodies to virus capsid antigen; the EBV genome was detected in lymphoreticular tissues by molecular hybridization studies in two cases. Nine days after starting the sulphasalazine + methotrexate (MTX) combination, given inappropriately for a presumed flare-up of SOJCA, a 7-yr-old boy developed high fever, dizziness, rash, vomiting and diarrhoea. Haemodynamic instability necessitated ICU admission. The syndrome did not respond to high-dose steroids. Intravenous cyclosporin A (CSA) was begun at a dose of 4 mg/kg/day. Fever abated within 24 h and the complete blood count normalized on day 5. He was discharged on day 26. CSA was discontinued on day 90 and no relapse occurred. The JCA was still active after 2 yr of follow-up.

Conjoint administration of ibuprofen and morniflumate or the introduction of morniflumate in a girl with SOJCA was thought to be the precipitating event in one case. In three cases, varicella-zoster virus (VZV) infection preceded the reactive syndrome. Intravenous aciclovir was used in each case but failed to alter the course of RHS.

In one patient treated with MTX, *Pneumocystis carinii* pneumonia (PCP) was complicated by RHS. The other putative aetiological factors are listed in Table 2.

### *Laboratory investigations (Table 3)*

Hypofibrinogenaemia was found in every patient. Eight patients had a factor I level below 1 g/l. A moderate deficiency of factors II and VII + X was observed in 20 patients, with a slight decrease in factor V values (data not shown). Liver dysfunction and high concentrations of triglycerides were observed consistently. The leucocyte count varied greatly from one patient to another. The lowest polymorphonuclear cell count was 1200/$\mu$l. Thrombocytopenia (defined as a platelet count below 150 000/$\mu$l) was also found consistently. Eight patients had a platelet count below 50 000/$\mu$l and 15 had a count below 100 000/$\mu$l (mean = 83 000/$\mu$l, S.D. = 61 900). Peripheral blood contained normochromic and normocytic erythrocytes with a low reticulocyte response.

TABLE 3. Laboratory investigations

| Biological data | Mean (S.D.) |
|---|---|
| Haemoglobin (g/dl) | 8.78 (1.38) |
| Fibrinogen (g/l) | 1.8 (1.14) |
| Platelets (no./$\mu$l) | 86 000 (65 000) |
| Alanine aminotransferase ($\times$normal) | 16.3 (21.7) |
| Triglyceridaemia (mmol/l) | 4.54 (1.50) |
| No. of patients with platelets $<50\,000/\mu$l at diagnosis | 8 |
| No. of patients with platelets $<100\,000/\mu$l at diagnosis | 15 |
| Haemophagocytosis (marrow) | 14/17 |
| CSF hypercellularity | 2/6 |

Marrow smears were evaluated in 17 cases and showed normal or increased cellularity with active haematopoiesis. Haemophagocytic histiocytes were found in 14 smears; an increased number of plasma cells was found in three and dyserythropoietic changes in eight.

Because of low platelet counts, only six of the patients presenting neurological dysfunction underwent CSF studies. Pleiocytosis with macrophages and lymphocytes was found in two cases.

### *Treatment and outcome*

The 24 patients had 29 episodes of RHS (three patients each had two episodes and one patient had three episodes). Ten children were already on oral steroids at the onset of RHS. Intravenous steroids (ranging from a conventional dose of 0.75–2 mg/kg/day to pulse methylprednisolone at 1 g/m$^2$ per injection) were used as initial therapy for 21 of the 29 episodes. Fifteen patients improved within 5–15 days of therapy. The course of one case involving VZV is illustrated in Table 4.

The seven patients in whom steroids ($>5$ mg/kg/day in six cases, $<3$ mg/kg/day in three cases) failed received CSA salvage therapy and all entered full remission. The dose and route of CSA varied (3–7 mg/kg/day; i.v. in four patients and oral in two); trough levels were between 200 and 400 ng/ml. Intravenous CSA was used as first-line therapy in five patients, either alone or together with the steroid regimen that was being used at the onset of RHS. Remission was obtained in every case. CSA treatment was well tolerated except in two cases (one case of mild hypertension and one of moderate elevation of serum creatinine that reversed on dose reduction). Immunoglobulins were used for initial treatment in four cases and no response was obtained.

One patient was treated with etoposide in addition to i.v. steroids after failure of steroids, as mentioned above. Remission was transient. Four children had relapse of the haemophagocytic syndrome (one relapse in three cases, two relapses in one case). Details of these patients are shown in Table 5. Remission was maintained in all other patients. The course of the underlying disease was variable. In most patients ($n=20$) the disease remained active and severe.

TABLE 4. The effects of steroids on clinical and biological findings in a patient with VZV-associated RHS

| | Days of steroid treatment | | | |
|---|---|---|---|---|
| | 0 | 3 | 10 | 17 |
| Coma (Glasgow scale) | 3 | 7 | 13 | |
| Haemorrhage[a] | +++ | ++ | + | |
| Alanine aminotransferase[b] (U/l) | 530 | 187 | 45 | 18 |
| Aspartate aminotransferase[c] (U/l) | 30 | 59 | 55 | 40 |
| Triglycerides (mmol/l)[d] | 4.75 | 4.65 | 4.05 | 2.4 |
| Platelets ($10^3/\mu$l) | 40 | 33 | 113 | 137 |
| Fibrinogen (g/l) | 0.95 | 0.3 | 1.4 | 2.9 |
| Plasma TNF-$\alpha$ (pg/ml) | 392 | 323 | 118 | $<0.01$ |
| Urine TNF-$\alpha$ (pg/ml) | 293 | 287 | 349 | $<0.01$ |
| Steroids (mg/kg/day) | 5 | 5 | 3 | 2 |

TNF-$\alpha$, tumour necrosis factor $\alpha$.
[a]+++, spontaneous mucosal and cutaneous haemorrhage; ++, diffuse ecchymotic purpura; +, petechial purpura.
[b]Normal $<30$ U/l.
[c]Normal $<30$ U/l.
[d]Normal range 0.35–0.99 mmol/l.

Two children (8%) died—the patient whose history is summarized above and a 13-yr-old with a 7-month history of SLE. Whilst on chloroquine, prednisone (40 mg/day) and azathioprine (100 mg/day), she developed fever and congestive heart failure. A bone marrow aspirate revealed intense haemophagocytosis. Despite broad-spectrum antibiotics, high-dose steroids (3 mg/kg/day) together with i.v. immunoglobulin, then bolus methylprednisolone, she died with uncontrolled cardiogenic shock and pulmonary oedema 4 days after onset. No triggering event could be identified.

An underlying immunodeficiency was sought in all patients who survived and entered remission (blood T and B lymphocyte counts, proliferative responses to vaccinal antigens, serum IgG, A and M; data not shown). Only one patient, the child with *Pneumocystis carinii* pneumonia, had an underlying IgA + IgG2 deficiency.

## Discussion

RHS is characterized by multisystem infiltration by macrophages and lymphocytes, accompanied by high plasma concentrations of soluble mediators of macrophage origin. Lymphokines secreted by lymphoid cells may be responsible for the systemic activation of mononuclear phagocytes [7, 8]. RHS has been documented in children in association with viral, bacterial, fungal and parasitic infections (the so-called infection-associated haemophagocytic syndrome) [4, 9, 10] as well as in the context of a broad spectrum of malignancies, and genetic disorders such as Chédiak–Higashi disease [12] and familial erythrophagocytic lymphohistiocytosis [3].

All the acutely ill patients in this cohort had an abnormal coagulation profile, elevated liver enzyme levels, high triglyceride levels, low plasma fibrinogen levels and a fall in the platelet count, which is in keeping with a diagnosis of RHS [4, 12]. Biopsy evidence of haemophagocytosis was obtained in only 15 patients

Table 5. Clinical and laboratory features, treatment and outcome in four patients who relapsed

| Patient | Sex, age (yr) and underlying condition | RHS symptoms | Treatment at time of presentation | Outcome |
|---|---|---|---|---|
| 1 | F, 10 yr, polyarticular JCA | 1st episode: paradoxical improvement of polyarthritis, spleen & liver enlargement, fever | Oral steroids + NSAIDs | Full remission after 10 days with i.v. methylprednisolone 3 mg/kg/day, replaced with oral steroids |
| | | 2nd episode 3 months after 1st; haemophagocytic panniculitis | Oral steroids | Full remission after 1 week of oral CSA |
| | | 3rd episode 6 months later: haemophagocytic panniculitis | Oral CSA with low CSA trough levels | ↑ oral CSA, full remission after 4 days |
| 2 | M, 12 yr, SOJCA | 1st episode[a]: myalgias, fever, left pneumonia, respiratory distress, mild pleuritis, pericarditis, widespread purpura, lethargy | No treatment during previous 3 yr | Failure with i.v. Ig + i.v. steroids: 5 mg/kg/day<br>Prompt remission with addition of i.v. CSA |
| | | 2nd episode: relapse at 1 month | Oral corticosteroids/CSA | Prompt remission with i.v. CSA/i.v. corticosteroids |
| 3 | F, 6 yr, SOJCA | 1st episode: high fever, adenomegaly, melena, alveolar pneumonitis, respiratory distress, coma, ICU admission, haemorrhagic diathesis | Diclofenac | Failure with i.v. steroids 3 mg/kg/day<br>Prompt remission with addition of i.v. CSA |
| | | 2nd episode at 2 months on reducing steroids and CSA | Oral CSA/corticosteroids with low CSA trough levels | Full remission with ↑ CSA |
| 4 | M, 16 yr, polycyclic systemic disease | 1st episode[b]: myalgia, headache, fatigue, stomatitis | Indomethacin + steroids | Full remission with i.v. steroids 2 mg/kg/day |
| | | 2nd episode: fatigue, weight loss (−4 kg), pruritus, myalgia, night fever, vomiting 1 yr after discontinuation of CSA | Diclofenac | Adjunction of CSA for 1 yr<br>Stopped diclofenac<br>Oral steroids 3 mg/kg/day + oral CSA induced full remission<br>Upsurge in inflammatory disease |

Underlying disease was still active at 9, 6, 6, 7 yr follow-up for patients 1, 2, 3 and 4 respectively.
[a]Patient was in remission at the time of the 1st episode of RHS.
[b]EBV infection may have been a possible trigger for the 1st episode.

(14 out of 17 patients with marrow aspirates and one patient with liver necropsy) among the 31 episodes of RHS described. In our opinion, RHS can reasonably be diagnosed on the basis of the clinical features and laboratory findings—which are highly atypical with regard to the usual course of inflammatory diseases—together with a favourable response to immunosuppressive therapy when bone marrow haemophagocytosis has not been detected or sought. In addition, the absence of this cytological criterion must not be allowed to delay treatment, which is urgently required.

Disseminated intravascular coagulopathy was the most commonly reported cause of death in arthritic children [13], particularly when associated with intramuscular gold treatment [13–16]. Hadchouel *et al.* [17] described seven new cases in 1985, and were the first authors to suggest that an inappropriate reactive histiocytic process is responsible for this pathophysiology. Children with JCA, particularly those with SOJCA, appeared to be the most susceptible group [18], which was confirmed in our cohort. Adults have also been reported to be prone to this complication [19]. The lymphohistiocytic syndromes complicating lupus and panniculitis have similar clinical and biological features [20].

RHS is life-threatening yet poorly understood. Two observations from our cohort illustrate the potentially fulminant course. It is sometimes diagnosed late because it masks a flare-up of disease or an infection. Ten of our patients had to be admitted to the ICU because of circulatory failure, multiorgan failure or respiratory involvement (present in half the patients), which warranted mechanical ventilation. Cardiac involvement (akinetic cardiomyopathy, pericardial effusion, etc.) was very common. Renal involvement had not been reported previously in haemophagocytic syndromes. The altered glomerular permeability, illustrated by a sudden rise in the creatinine concentration in a few patients, may have resulted from detrimental effects of cytokines and/or activated inflammatory cells on the glomeruli. CNS disorders, with seizures, behavioural disturbances and an abnormal EEG, have occasionally been described in SOJCA [21]. The cases in the present study sometimes had CNS involvement, which was presumably multifactorial (effect of cytokines on the CNS, haemodilution, meningeal infiltration, etc.). In familial haemophagocytic lymphohistiocytosis (the prototype of haemophagocytic syndrome), oedema, meningeal involvement with infiltration by lymphocytes and macrophages, and perivascular infiltrates are prominent neuropathological findings, with haemophagocytosis in the leptomeninges [22].

Haemophagocytic syndrome seems to be a risk at any time when there is ongoing underlying systemic disease. Our findings confirm reports in the literature suggesting the catalytic role of recent infection (EBV in reference

[23] and four patients in the present series; VZV [24]; hepatitis A virus [25]; and Coxsackie virus [26]). This may be indicative of defective immune responses to infections in these forms of systemic disease. In one of our patients, PCP might have been the triggering event; the protozoan *P. carinii* is increasingly reported in adults treated for connective tissue disease with steroids and cyclophosphamide or MTX, and occasionally in children [27]. It has also been suggested that MTX can cause immunological dysfunction, triggering inappropriate lymphohistiocytic activation. Other potential triggers are anti-inflammatory drugs, which must be handled with caution in these fragile children. Ten cases reported in the literature suggest that a second gold salt injection activated macrophages and triggered the syndrome [17]. Gold-particle phagocytosis has been described in patients with rheumatoid arthritis who were given gold therapy in the form of lysosomal microcrystals [28]. Gold retention by macrophages might activate these cells. Slow-acting agents, such as Salazopyrin (sulphasalazine) and gold, should probably be avoided or used with great caution in these patients [29, 30]. Non-steroidal anti-inflammatory drugs (NSAIDs), aspirin and the aspirin–indomethacin combination have also been incriminated. Salicylate toxicity, which is particularly a risk when high doses are given and/or with hypoalbuminaemia must be looked for carefully.

Hypofibrinogenaemia, contrasting with a moderate fall in factors V and VII + X (a consistent feature in this series) is caused by the direct action of activated macrophages on factor X through the integrin Mac (CD116/CD18) and subsequent activation of the common pathway of the coagulation protease cascade, and uptake of fibrin and/or fibrinogen [31]. Hypofibrinogenaemia explains the unusually low erythrocyte sedimentation rate, a strikingly unusual feature in inflammatory diseases that may produce a false sense of security in the clinician if it is used as a parameter to monitor the activity of an underlying inflammatory disorder. Too few patients underwent full clotting studies. Hence the part played by liver dysfunction, disseminated intravascular coagulation or vitamin K deficiency could not be determined. Serum triglyceride levels were markedly elevated during the active phase in our patients and declined when therapy was successful, but often this did not occur until more than 1 month after the episode (data not shown). It has been suggested that elevated inflammatory cytokine levels, which were found in each of the two patients tested, contribute to the generation of the biological abnormalities observed in RHS, including the suppression of lipoprotein lipase activity.

Impaired liver function may also have contributed to the coagulation disorders seen in the present study. Hepatomegaly and liver dysfunction are common in RHS. Kupffer cell hyperplasia with prominent haemophagocytosis in liver biopsy specimens was indicative of RHS in the only patient who was autopsied [32].

There is no agreed treatment protocol for RHS in patients with systemic disease. Thus, treatment was chosen by each primary caregiver. There was general agreement that fluid–electrolyte imbalance and coagulation disorders (afibrinogenaemia and thrombocytopenia) must be corrected and intensive care instituted for patients with multiorgan failure. Infections should be treated, particularly where there is a specific treatment such as aciclovir for chickenpox and, possibly, EBV infection. Polyvalent immunoglobulin has been reported to be effective [33, 34] but seemed unhelpful in our series. NSAIDs should be discontinued. The immediate introduction of high-dose steroids or a dose increment of ongoing steroids, even in cases of systemic viral infection, seemed very effective in the present study. Steroids were successful in 15 but failed in six episodes. Etoposide (VP16) was used in only one patient, and gave a short-lived remission. In the light of the report of secondary malignancies such as myelodysplastic syndromes and acute myelocytic leukaemia following etoposide therapy [35], caution should be exercised in its use in this indication. By contrast, CSA appears to be remarkably effective and consistently active whatever the route of administration. Like others, we found that CSA combined with antithymocyte globulins and steroids readily induced remission in children with familial erythrophagocytic lymphohistiocytosis [36, 37]. CSA seemed to be generally safe in this group of patients and did not affect the course of the underlying disease adversely (results not shown), although it is unclear exactly when CSA should be introduced, or for how long treatment should be given. We suggest that, in cases of life-threatening situations, CSA may be either used as the first-line treatment or added later if rapid improvement does not occur with steroids at or 2 mg/kg/day or a higher dose. It can be argued that patients should remain on therapy as long as biological abnormalities (hypertriglyceridaemia, low fibrinogen and/or elevated liver enzyme levels) persist.

The adverse effects of CSA (renal and hepatic dysfunction, hypertension and infection) can usually be ameliorated by monitoring and prompt treatment. The efficacy of CSA in a case of reactive haemophagocytic syndrome after treatment with MTX has been described recently [28]. However, it is noteworthy that the patient developed PCP 2 months later.

This observational study illustrates that RHS may be a more common complication of systemic disease in childhood than has been reported previously, especially in the context of SOJCA. This life-threatening event may complicate active inflammatory diseases at any stage of their course and calls for the immediate withdrawal of potentially triggering medications, anti-infective therapy when relevant, and the prompt introduction of corticosteroids or CSA or both.

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