Adult haemophagocytic syndrome

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Haemophagocytic syndromes (haemophagocytic lymphohistiocytosis) have a wide range of causes, symptoms, and outcomes, but all lead to a hyperinflammatory response and organ damage—mainly reported in paediatric patients, but reports of adult presentation are increasing. Analysis of the genetic and molecular pathophysiology of these syndromes have improved the understanding of the crosstalk between lymphocytes and histiocytes and their regulatoty mechanisms. Clinical presentations with a broad differential diagnosis, and often life-threatening outcome, complicate the management, which might include supportive intensive care, immunosuppressive and biological treatments, or haemopoietic stem cell transplantation. Insufficient knowledge of these syndromes could contribute to poor prognosis. Early diagnosis is essential to initiate appropriate treatment and improve the quality of life and survival of patients with this challenging disorder.

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For the **Histiocyte Society website** see http://www.histiocytesociety.org

Introduction

Haemophagocytic syndrome is an immune-mediated life-threatening disease, which was first described in 1939 by paediatricians Scott and Robb-Smith,[1] and is caused by impaired natural killer and cytotoxic T-cell function. Clinically, the syndrome is characterised by fever, hepatosplenomegaly, and cytopenia and the finding of activated macrophages in haemopoietic organs. It has been given several different names, including macrophage activation syndrome, which was used for patients with rheumatological diseases such as juvenile idiopathic arthritis.[2] In 1991, the Histiocyte Society proposed the name haemophagocytic lymphohistiocytosis.[3]

Haemophagocytic lymphohistiocytosis can occur at any age, but most clinical guidelines, prospective studies, and treatment trials have focused on paediatric patients. Little scientific analysis of adult haemophagocytic lymphohistiocytosis has been done, although an observational study[4] in almost 300 Japanese hospitals identified that 40% of haemophagocytic lymphohistiocytosis cases occur in adults. This Seminar updates our current knowledge of haemophagocytic lymphohistiocytosis and focuses mainly on clinical aspects that might help specialists treating adults with haemophagocytic lymphohistiocytosis.

Epidemiology

Haemophagocytic lymphohistiocytosis is a rare disease, with an estimated yearly incidence of one per 800 000 people and one to ten per 1 million children in Italy, Sweden, and the USA.[5–8] Geographical variability is a key epidemiological characteristic of haemophagocytic lymphohistiocytosis. Figure 1 summarises the country of origin and causes of 2197 reported (panel 1) cases of adult haemophagocytic lymphohistiocytosis—identified in our search strategy—of which almost 50% are in Japan. The predominant cause differs in each country, which suggests a specific genetic background or differences in suspected triggering agents, particularly infections.[9] Haemophagocytic lymphohistiocytosis in some patients with primary viral infection occurs after travel abroad.[10,11] The epidemiological profile of an adult with haemophagocytic lymphohistiocytosis is not well defined. We reviewed the clinical characteristics of 775 (panel 1) of 2197 reported cases[12–39] and identified a male:female ratio of 1:7 and a mean age at diagnosis of almost 50 years (table 1).

Causes

Haemophagocytic lymphohistiocytosis has traditionally been classified according to the cause of disease and is divided into primary (genetic) and secondary (reactive), which are subclassified as viral, autoimmune, or neoplasia related;[40] although nearly a third of reported cases in adults have more than one underlying cause. In children, underlying genetic defects play a predominant part in the development of haemophagocytic lymphohistiocytosis. In adults, the two main groups of causative factors are external (infections and drugs); these either initiate disease or are underlying diseases or disorders that increase the risk of haemophagocytic lymphohistiocytosis (panel 1, figure 2).

Search strategy and selection criteria

We searched Medline and Embase for articles published from Jan 1, 1974, to Sept 29, 2011, with the term "hemophagocytic syndrome". We selected articles that included adult cases (age >17 years) in which the cause of haemophagocytic syndrome was clearly detailed. Duplicate publications, paediatric cases, experimental studies, and articles with incomplete or irrelevant information were excluded. We selected articles that described clinical series in adults (including at least ten patients) to gather information on the clinical presentation, and articles that analysed specific treatment interventions in which the response to treatment was detailed. We also manually searched the reference list of relevant articles retrieved. Study designs were considered in the following order (listed from highest to lowest evidence quality): controlled trials, prospective cohort studies, case-control studies, retrospective studies, and case series. Appendix p 1 shows a flow diagram of our search results.

See Online for appendix

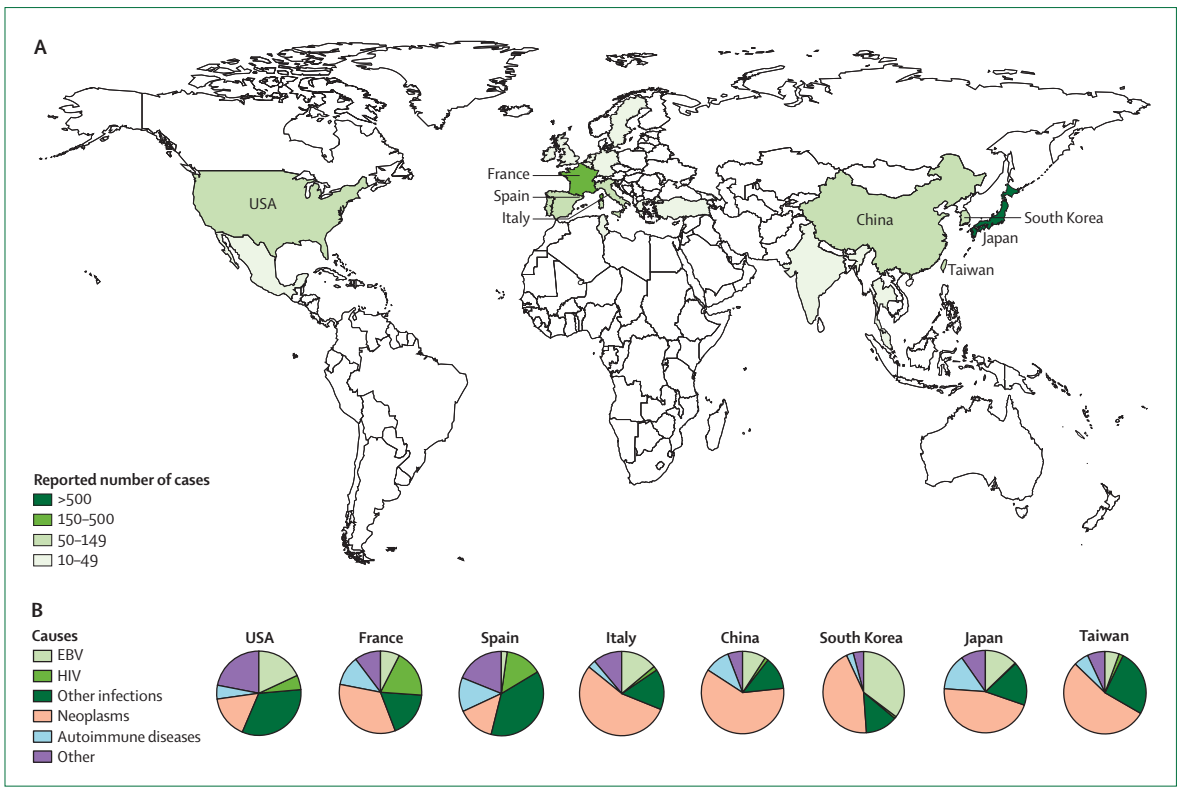

Figure 1: **Country of origin (A) and cause (B) of 2197 reported cases of haemophagocytic lymphohistiocytosis in adults (panel 1)**
EBV=Epstein-Barr virus.

Triggers

Haemophagocytic lymphohistiocytosis has infectious and non-infectious triggers. Viral infection is the most frequent trigger, either as a primary infection in healthy people or after reactivation in immunosuppressed patients. Herpes viruses account for 62% of reported viral cases of haemophagocytic lymphohistiocytosis in adults (panel 1). 43% of the viral cases are due to Epstein-Barr virus (EBV) and 9% to cytomegalovirus. Of the non-herpes viruses, more than ten cases were acute hepatitis A, parvovirus B19, and influenza; haemophagocytic lymphohistiocytosis has been reported as the cause of death in patients infected with influenza H1N1 or H5N1 strains.[41] Specific geographical distribution occurs, with EBV the predominant virus in Asia and the USA, and HIV in Europe (figure 1).

Bacterial infections are reported in 9% of adult cases of haemophagocytic lymphohistiocytosis, of which 38% were due to tuberculosis (panel 1). More than half of the cases related to tuberculosis had underlying comorbidities and more than 80% had extrapulmonary disease, with a mortality rate of nearly 50%.[42] Haemophagocytic lymphohistiocytosis has also been reported after adjuvant intravesical or BCG vaccination.[43,44] Among non-mycobacterium infections, more than ten cases have been reported for *Rickettsia* spp, *Staphylococcus* spp, and *Escherichia coli* (panel 1).

Parasites and fungi are less frequent triggers of haemophagocytic lymphohistiocytosis, with histoplasma, leishmania, plasmodium, and toxoplasma being the most frequently reported (panel 1). A travel history is crucial in the identification of the triggering agent in immunocompetent patients who have returned from endemic regions, whereas haemophagocytic lymphohistiocytosis is often related to opportunistic infections in immunosuppressed patients (*Pneumocystis jiroveci*, *Toxoplasma gondii*, and fungi).[41]

Although haemophagocytic lymphohistiocytosis is mainly related to external infectious triggers, it has also been associated with some drugs (appendix p 2). Other isolated triggers include vaccination, surgery (splenectomy, cardiac surgery, colectomy, hepatic resection, and post partum), and severe burns.[2,15]

Predisposing factors

Patients with cancer are prone to haemophagocytic lymphohistiocytosis, mainly those with haematological neoplasms, especially lymphoma. Machaczka and coworkers[45] estimated that haemophagocytic lymphohistiocytosis affects 1% of adults with haematological cancer, but the prevalence rises to 20% in patients with some types of B-cell (intravascular form or presenting without peripheral adenopathies) and T-cell lymphoma (nasal natural-killer-cell or panniculitis-like;

appendix p 3). Haemophagocytic lymphohistiocytosis has also been reported in patients with non-lymphoma haematological neoplasms and, less frequently, in solid organ cancers. Intensive chemotherapy can enhance susceptibility to infection, and some cancers are closely related to specific viral triggers (T-cell lymphoma is associated with EBV and multicentric Castleman's disease is associated with HIV and human herpesvirus-8 co-infection). In patients with cancer without any identifiable infectious triggers, the cause and development of haemophagocytic lymphohistiocytosis has been linked to excessive cytokine secretion by tumour cells.[2]

Of more than 30 systemic or organ specific autoimmune diseases associated with haemophagocytic lymphohistiocytosis, two are closely associated: systemic lupus erythematosus and adult-onset Still's disease. More cases of systemic lupus erythematous associated with haemophagocytic lymphohistiocytosis have been reported than have cases of adult-onset Still's disease (133 *vs* 54, respectively), but the prevalence of haemophagocytic lymphohistiocytosis is higher in adult-onset Still's disease (12% *vs* 4%, appendix p 3). Less frequently, haemophagocytic lymphohistiocytosis has been reported in patients with rheumatoid arthritis, systemic vasculitides, or inflammatory bowel disease.[12,24,30] The reported triggers of haemophagocytic lymphohistiocytosis in patients with these diseases are mainly infections and, less frequently, concomitant drugs.

Haemophagocytic lymphohistiocytosis has been reported in patients with chronic viral infections. The best example is in adults with HIV, of whom 173 cases had the disease (panel 1). A review[46] showed that most patients with haemophagocytic lymphohistiocytosis and HIV are substantially immunosuppressed (>80% have a CD4 cell count <2x10^8 cells per µL). In patients with HIV, haemophagocytic lymphohistiocytosis might be triggered by opportunistic or non-opportunistic infections, or related to neoplasms or the initiation of highly active antiretroviral therapy in about 70% of cases, whereas nearly 30% have no apparent trigger or underlying disease.[46] More infrequently, haemophagocytic lymphohistiocytosis has been reported in

***Panel 1*: List of triggers and associated diseases and processes detailed in 2197 adult haemophagocytic lymphohistiocytosis cases identified through search strategy**

Infection (1108)

a) Viruses (762)
- Epstein-Barr virus (330)
- HIV (173)
- Herpes viruses (74)
- Cytomegalovirus (69)
- Viral hepatitis (20)
- Influenza (14)
- Human parvovirus B19 (14)
- Other viruses or not specified (68)

b) Bacteria (206)
- *Mycobacterium tuberculosis* (78)
- *Rickettsia* spp (17)
- *Staphylococcus* spp (15)
- *Escherichia coli* (11)
- Other bacteria or not specified (85)

c) Parasites (53)
- *Leishmania* spp (17)
- *Plasmodium* spp (14)
- *Toxoplasma* spp(10)
- Other parasites (12)

d) Fungi (37)
- *Histoplasma* spp (18)
- Other fungi (19)

e) Infection not specified (50)

Neoplasms (1047)

a) Haematological (981)
- T-cell or natural-killer lymphoma (369)
- B-cell lymphoma (333)
- Leukaemia (67)
- Hodgkin's lymphoma (61)
- Not specified lymphoma (35)
- Castleman's disease (22)
- Other haematological neoplasmsor not specified (94)

b) Solid (32)

c) Not specified neoplasm (34)

Autoimmune diseases (276)

a) Systemic (244)
- Systemic lupus erythematosus (133)
- Adult-onset Still's disease (54)
- Rheumatoid arthritis (18)
- Vasculitis (11)
- Other or not specified (28)

b) Organ-specific (32)
- Inflammatory bowel disease (11)
- Other diseases (21)

Other circumstances or diseases (184)

a) Transplantation (95)
- Kidney (53)
- Haematological (29)
- Other (13)

b) Other circumstances (76)
- Drugs (20)
- Surgery or biopsies (11)
- Vaccination or acute injuries (10)
- Diabetes or chronic liver disease (14)
- Pregnancy (11)
- Haemodialysis (10)

c) Other or not specified (13)

Idiopathic or unknown (81)

Number of reported cases in parentheses.

patients with chronic hepatitis B virus or hepatitis C virus infection.

The same virus can act as either an acute trigger in some patients or as an underlying predisposing disease in patients with chronic infection. Thus, haemophagocytic lymphohistiocytosis has been associated with acute primary infection caused by typically chronic viruses (HIV, hepatitis B virus, and hepatitis C virus), whereas some viruses overwhelmingly reported as acute triggers (EBV and cytomegalovirus) cause haemophagocytic lymphohistiocytosis due to reactivation of chronic infection.[47]

Both haematological and solid organ transplantation are associated with haemophagocytic lymphohistiocytosis. In patients undergoing haematopoietic stem cell transplantation, the estimated frequency of haemophagocytic lymphohistiocytosis is higher in those receiving umbilical cord blood transplant (17%) than in those receiving autologous or allogeneic transplant (<1%) (appendix p 3). In patients receiving solid organ transplants, especially kidneys, retrospective studies[14,48,49] have estimated a frequency of haemophagocytic lymphohistiocytosis of 0·4–2%. In transplant recipients, haemophagocytic lymphohistiocytosis is often associated with severe opportunistic infections, although some cases have been reported in the setting of primary graft failure.

Haemophagocytic lymphohistiocytosis has been reported in pregnant women and patients with underlying diseases, including chronic renal or liver disease, diabetes mellitus, chronic granulomatous disease, and pernicious anaemia.

Pathophysiology

A defect in granule mediated cytotoxicity, which is important in killing cells,[50] is the underlying common mechanism in both genetic and reactive forms of haemophagocytic lymphohistiocytosis. The perforin and Fas systems play a part in the maintenance of homoeostasis of dendritic cells and restrict T-cell activation by antigen presentation.[51] Enhanced antigen presentation and repeated interferon γ-dependent stimulation of Toll-like receptors are postulated as causal mechanisms of the uncontrolled activation of

	Patients (N=775)
Epidemiological features	
Mean age (range)	49·03 years (41–67 years)
Women	275/746 (37%)
Clinical features	
Fever	524/546 (96%)
Splenomegaly	420/609 (69%)
Hepatomegaly	389/580 (67%)
Pulmonary involvement	61/145 (42%)
Peripheral adenopathies	91/277 (33%)
Neurological involvement	41/161 (25%)
Skin lesions	63/250 (25%)
Gastrointestinal involvement	27/149 (18%)
Renal involvement	9/56 (16%)
Encephalopathy	9/102 (9%)
Haematological and coagulation features	
Anaemia	
Haemoglobin <5·6 mmol/L	122/181 (67%)
Haemoglobin <4·3 mmol/L	33/151 (22%)
Thrombocytopenia	
<100 000 cells per mm³	178/227 (78%)
<10 000 cells per mm³	10/168 (6%)
Leukopenia <4000 cells per mm³	198/285 (69%)
Neutropenia	
<1000 cells per mm³	61/144 (42%)
<500 cells per mm³	15/64 (23%)
Coagulopathy	91/153 (59%)
D-dimer >54·8 mmol/L	24/49 (49%)
Fibrinogen <4·4 µmol/L	39/81 (48%)
Disseminated intravascular coagulation	40/101 (40%)
(Continues in next column)	
(Continued from previous column)	
Biochemical features	
Ferritin	
>1123·5 pmol/L	178/198 (90%)
>2247 pmol/L	164/230 (71%)
>22 470 pmol/L	40/170 (24%)
Triglycerides	
>1·7 mmol/L	132/192 (69%)
>3·0 mmol/L	42/100 (42%)
Hyponatraemia	
<135 mmol/L	57/73 (78%)
<130 mmol/L	10/17 (59%)
Raised transaminases (ALT and AST)	
>40 IU/L	164/286 (57%)
>100 IU/L	48/115 (42%)
Alkaline phosphatase >290 UI/L	66/93 (71%)
Increased lactate dehydrogenase	
>500 IU/L	190/243 (78%)
>1000 IU/L	81/152 (53%)
Increased sILR2	
>2400 IU/mL	95/120 (79%)
>10 000 IU/mL	45/120 (38%)
Haemophagocytosis	
Positive bone marrow aspirate	257/304 (85%)
Positive bone marrow biopsy	14/22 (64%)

Data are n/N (%) or mean (range). Variables are not detailed in all cases, and the prevalence of a specific feature has been stated as number of cases with that feature (numerator)/number of cases in which the feature was detailed (denominator). ALT=alanine aminotransferase. AST=aminotransferase. sILR2=soluble interleukin 2 receptor.

Table 1: **Main epidemiological, clinical, histopathological, and laboratory features of of 775 adult patients with haemophagocytic lymphohistiocytosis included in the main reported series including more than ten cases[12–39]**

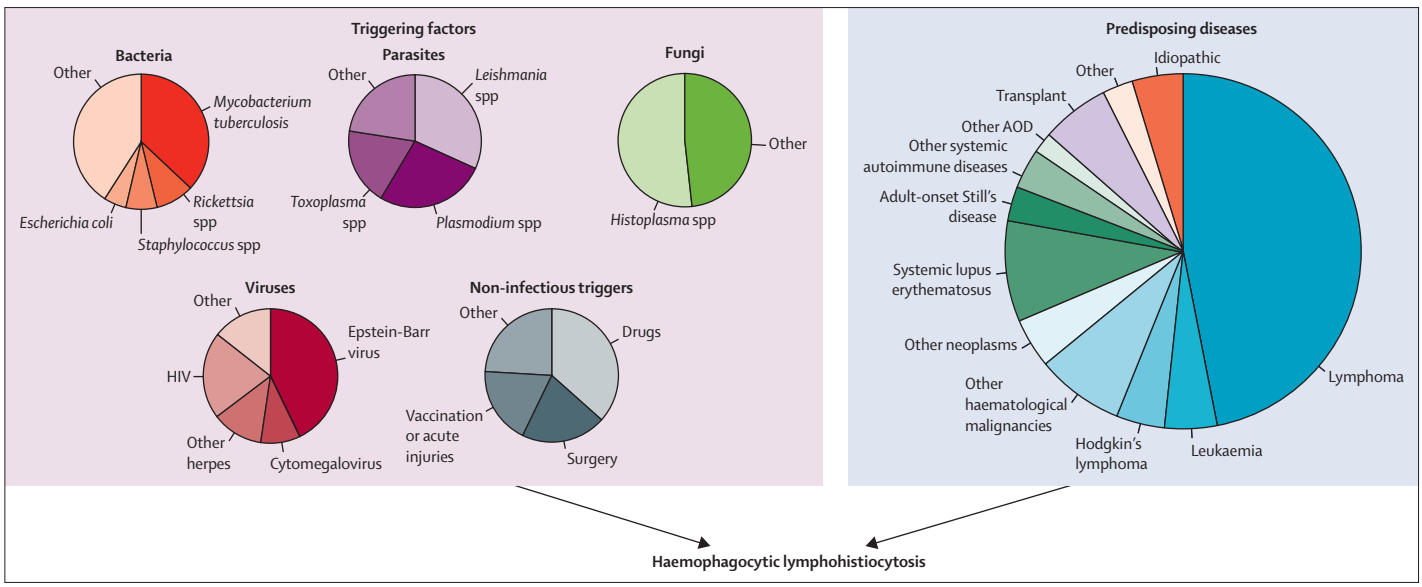

Figure 2: **Main triggering factors and predisposing diseases of haemophagocytic lymphohistiocytosis in 2197 cases reported in adults (panel 1)**

antigen-presenting cells (macrophages and histiocytes) and T cells.[52–54] This activation produces an exaggerated inflammatory response caused by hypersecretion of proinflammatory cytokines such as interferon γ, tumour necrosis factor α (TNFα), interleukin 1, interleukin 4, interleukin 6, interleukin 8, interleukin 10, and interleukin 18.[55–57] This so-called cytokine storm could be pathogenically related to the development of the main clinical and laboratory features of haemophagocytic lymphohistiocytosis[52] and contributes to tissue damage and progressive systemic organ failure.

Clinical presentation

The first symptoms of haemophagocytic lymphohistiocytosis are non-specific with a generally acute or subacute (1–4 weeks) clinical presentation.[13,19,21] The cardinal features are continuous high fever (>38·5°C) and enlarged lymphohaemopoietic organs (adenopathies and hepatosplenomegaly) on examination. A quarter of adult patients might also have non-specific cutaneous involvement, including erythematous rashes, oedema, petechiae, or purpura; special attention should be paid to subcutaneous, panniculitic-like nodules because of the close association with underlying T-cell lymphoma.

Internal organ involvement is frequent and often leads to progressive multiple organ failure,[12–39] with intensive care needed in nearly half of patients.[16,32] The spleen and liver are the most frequently involved organs;[12–39] (table 1) nearly 60% of patients have altered liver tests, and haemophagocytic lymphohistiocytosis can present in adults as encephalopathy, ascites, veno-occlusive disease, or non-traumatic splenic rupture.[23,58,59] Pulmonary involvement is frequent (42%), and symptoms can include cough, dyspnoea, and respiratory failure,[14,29] especially in cases triggered by respiratory viruses. Non-specific gastrointestinal symptoms (18%) include diarrhoea, nausea, vomiting, and abdominal pain,[14] with specific presentations including gastrointestinal haemorrhage, pancreatitis, or ulcerative bowel disease. Neurological presentations (25%) are heterogeneous and include coma, seizures, meningitis, encephalomyelitis, cavernous sinus syndrome, or cerebral haemorrhage.[12,14,29,60] Some patients might present with psychiatric changes, including mood disorders, delirium, or psychosis.[12,29] Other neurological presentations, such as Guillain-Barré or cauda equina syndromes have also been reported.[61] Renal involvement has been reported in 24 cases (appendix p 4)—mainly as renal failure (88%) or nephrotic syndrome (38%); renal biopsy disclosed mainly collapsing glomerulonephropathy (38%) and thrombotic microangiopathy (23%), with half of cases requiring haemodyalisis.

Internal organ involvement might be attributed to either the underlying disease, infectious triggers, or complications related to haemophagocytic lymphohistiocytosis itself. Thus, ulcerative bowel disease might be related to infectious triggers (cytomegalovirus) or an underlying process (inflammatory bowel disease), and CNS involvement to malaria or underlying lymphoma, whereas haemophagocytic lymphohistiocytosis-related complications might include haemorrhagic problems in any organ (caused by disseminated intravascular coagulation) or acute pancreatitis (caused by severe hypertriglyceridaemia).[62]

Diagnosis

Haemophagocytic lymphohistiocytosis should be suspected in patients presenting with unattributable, continuous high fever, and evidence of multiple organ involvement. Some laboratory findings might support the clinical suspicion together with histopathological

Panel 2: **Diagnostic features of haemophagocytic lymphohistiocytosis***

Epidemiological features
- Family history of haemophagocytic lymphohistiocytosis
- History of severe or recurrent Epstein-Barr virus infection
- Fever after travel abroad
- Patients from southeast Asia

Clinical findings
- High, persistent fever (>38·5°C)
- Peripheral adenopathies
- Hepatomegaly
- Splenomegaly
- Skin rashes
- Panniculitic-like cutaneous nodules
- Multiple involvement of internal organs

Laboratory abnormalities
- Severe bicytopenia or pancytopenia
- Increased liver tests (phosphatase alkaline and transaminases)
- Increased lactate dehydrogenase concentration
- Hypertriglyceridaemia
- Hyperferritinaemia
- Hyponatraemia
- Hypofibrinogenaemia
- Disseminated intravascular coagulopathy
- High soluble CD25 or CD163 concentrations

Histopathological findings
- Haemophagocytosis in bone marrow
- Haemophagocytosis in reticuloendothelial organs

*The more features of different subsets the patient presents, the greater the probability of a diagnosis of haemophagocytic lymphohistiocytosis.

evidence of haemophagocytosis (panel 2). Therefore, diagnosis of haemophagocytic lymphohistiocytosis relies on the coexistence of various clinical, laboratory, and histopathological findings, although none are pathognomonic alone. The diagnostic guidelines for haemophagocytic lymphohistiocytosis proposed by the Histiocyte Society in 1991[3] and updated in 2004[63] (panel 3) are widely used in adults, even though their sensitivity and specificity remain untested.

Laboratory abnormalities

Cytopenias are key laboratory markers of haemophagocytic lymphohistiocytosis and are mainly related to severe cytokine-mediated inflammation.[64] Thrombocytopenia and anaemia are identified in almost 80% of adult cases, and leukopenia in 69%. Severe anaemia (haemoglobin <4·34 mmol/L) or neutropenia (<5×10^8 cells per L) are reported in 20% of patients (table 1), with severe thrombocytopenia (<10^{10} cells per L) less frequent (6%). Positive Coombs tests and schistocytes are infrequent.

Almost 60% of patients have coagulation disorders related to liver dysfunction. Hypofibrinogenaemia (<441 mmol/L) and raised D-dimer levels (>54·76 nmol/L) are reported in 50% of adult haemophagocytic lymphohistiocytosis cases. Disseminated intravascular coagulation is reported in 40% of cases in some series and is associated with high mortality rates, especially in patients with severe thrombocytopenia.[15,18,26,27]

Nearly 80% of patients have altered liver test results (increased phosphatase alkaline and transaminase concentrations in 71% and 57%, respectively). Increased serum lactate dehydrogenase concentrations, caused by cell destruction, are reported in 78% of patients, and increased hyponatraemia is reported in the same percentage, sometimes associated with a syndrome of inappropriate antidiuretic hormone secretion.[65,66] Hypertriglyceridaemia (>1·67 mmol/L) is identified in 69% of adults with haemophagocytic lymphohistiocytosis and has been associated with lipoprotein lipase inhibition caused by excess TNF.[67]

Increased acute phase reactants (erythrocyte sedimentation rate or C-reactive protein concentration) are identified in 80–90% of patients, similar to other diseases causing systemic inflammation. However, hyperferritinaemia might play a major part in the differentiation of haemophagocytic lymphohistiocytosis from other systemic processes.[68] Possible causes of hyperferritinaemia in haemophagocytic lymphohistiocytosis include secretion of ferritin by macrophages or hepatocytes, release during erythrophagocytosis, or impaired clearance.[69] Ferritin concentrations of more than 1126·5 pmol/L are a classification criterion; 90% of adult patients with haemophagocytic lymphohistiocytosis have increased concentrations, and 24% have very high concentrations (22 470 pmol/L).

Identification of a triggering infectious agent is mandatory. The standard tests should be used to investigate infection with herpes viruses, which are identified in two-thirds of reported cases of haemophagocytic lymphohistiocytosis. Primary infection should be investigated mainly in young adults and immunocompetent people, whereas reactivations should be investigated in immunosuppressed adults. To clarify the triggering role of viral infections (especially those that are more frequent in adults), analysis of serum viral load by PCR might be more helpful than serology, the results of which should always be interpreted with caution (especially tests for the most common viral infections). A high serum EBV load might suggest a triggering role of EBV for haemophagocytic lymphohistiocytosis development because patients with infectious mononucleosis often have lower loads;[70] however, high loads might also be identified in patients with EBV-driven lymphomas as a marker of active neoplasia.[71] Other infectious agents (eg, *M tuberculosis*, parasites, fungi) should be ruled out according to specific clinical or epidemiological features.

Immunological studies

The abnormal immunological response caused by haemophagocytic lymphohistiocytosis can be measured either serologically or with functional cellular assays. Markers of macrophage activation (eg, β2 microglobulin, neuron specific enolase, neopterin, and transcobalamin II) and cytokines (eg, interferon γ, TNF α, and especially interleukin 18) are increased,[72,73] but the key diagnostic immunological markers are increased CD25 and CD163 concentrations and natural-killer (NK) cell activity. However, although included in the haemophagocytic lymphohistiocytosis classification guidelines, these tests might not be available in non-specialised centres,[2] even though they are accessible through referral laboratories.

High serum concentrations of soluble CD25 (interleukin 2 receptor α) occur in 79% of adult cases of haemophagocytic lymphohistiocytosis, and very high concentrations (>10 000 units per mL) in 37%. Measurement is made by standard ELISA, but the results can vary according to the assay used and the cut-off can be affected by age.[74]

Increased serum concentrations of soluble CD163 (a transmembrane haemoglobin and haptoglobin scavenger protein expressed on monocyte and macrophage surfaces) are identified in hyperinflammatory processes, although few data are available for adult patients with haemophagocytic lymphohistiocytosis.[75]

Low or absent NK cell activity is a criterion for diagnosis of haemophagocytic lymphohistiocytosis. NK cell function can be assessed with different methods (chromium 51 assays, CD107a mobilisation, or granzyme B proteolytic activity). However, some patients (especially children) who are critically ill might have normal results, which do not rule out the diagnosis of haemophagocytic lymphohistiocytosis.[70] These techniques have not been standardised in adults, although Chung and colleagues[76] reported lower NK cell activity in 13 adult patients with haemophagocytic lymphohistiocytosis than that in controls (8% *vs* 20%, respectively).

Histopathological studies

Haemophagocytosis, a physiological process that consists of phagocytosis of haematopoietic cells by activated macrophages (figure 3), is the key marker of haemophagocytic lymphohistiocytosis, but is not the only criterion for diagnosis, and should always be interpreted in the clinical context. Haemophagocytosis might be physiologically enhanced in some situations, including blood transfusions, infection, autoimmune diseases, and other causes of bone marrow failure or red blood cell destruction. Isolated organ-confined haemophagocytosis also occurs in the lymph nodes after surgery, and in the lung, liver, spleen, and skin (cytophagic histiocytic panniculitis).[2,36,77] The bone marrow is the preferred anatomical site for investigation of suspected haemophagocytic lymphohistiocytosis, with positive aspirates identified in 84% of reported adult cases. Analysis of bone marrow biopsy is less effective (64%) than aspirates, but might be useful to rule out underlying haematological neoplasia. Haemophagocytosis can also occur in the reticuloendothelial organs (lymph nodes, spleen, and liver) and occasionally in the skin or body fluids.[2,78] Unfortunately, there is no consensus on the differentiation of pathological haemophagocytosis from the physiological process.[77] Most studies in adults required that more than 2–3% of macrophages have signs of active haemophagocytosis for the diagnosis of haemophagocytic lymphohistiocytosis, with a median of six histiocytes counted per 500 nucleated cells;[77] however, a case-control study reported lower values of haemophagocytosis (0·082% in patients *vs* 0·009% in controls), with a sensitivity of 83% and a specificity of 60%.[79] Haemophagocytic activity might not occur at all in any organ during the disease course,[77] and might be absent in the initial phases of haemophagocytic lymphohistiocytosis or during dyserythropoiesis—in cases with high clinical and biological suspicion, repeat biopsies are recommended. However, the finding of haemophagocytosis should not be overestimated in the absence of other clinical or biological features suggestive of haemophagocytic lymphohistiocytosis.

Genetic defects involving proteins that play a key role in the control of granule mediated cytotoxicity pathways are related to development of haemophagocytic lymphohistiocytosis. Recent studies[80,81] have suggested the use of screening assays for protein products of

***Panel 3:* Diagnostic guidelines for haemophagocytic lymphohistiocytosis used in the HLH-2004 trial[63]**

Molecular diagnosis consistent with HLH

- Pathological mutations of *PRF1*, *UNC13D*, *STXBP1*, *RAB27A*, *STX11*, *SH2D1A*, or *XIAP*

OR

Five of the following criteria

- Fever of 38·5°C or more
- Splenomegaly
- Cytopenias (affecting at least two of three cell lineages in the peripheral blood)
  - Haemoglobin <5·59 mmol/L (infants <4 weeks, <6·21 mmol/L)
  - Platelets <100 cells per 10^9/L
  - Neutrophils <1 cell per 10^9/L
- Hypertriglyceridaemia (fasting, >3 mmol/L) and hypofibrinogenaemia (<1·7 mmol/L), or both
- Haemophagocytosis in bone marrow, spleen, lymph nodes, or liver
- Low or absent natural killer-cell activity
- Ferritin greater than 1123·5 pmol/L
- Increased soluble CD25 concentration (alpha chain of soluble interleukin 2 receptor)

HLH=haemophagocytic lymphohistiocytosis.

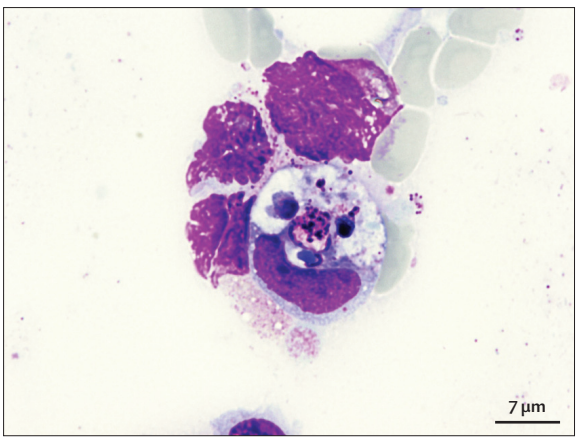

Figure 3: **May-Grünwald Giemsa-stained bone marrow aspirate**
Stained bone marrow aspirate shows a macrophage with phagocytised cells inside the cytoplasm in a 31-year-old woman with haemophagocytic lymphohistiocytosis, likely associated with an unidentified virus. Courtesy of Dr Maria Rozman, Pathology Department, Haematopathology Section, Hospital Clínic, IDIBAPS, University of Barcelona, Spain.

candidate genes (perforin, amyloid P component, and X-linked inhibitor of apoptosis) or degranulation assays. A resting NK-cell degranulation of less than 5% has a sensitivity and specificity of 96% and 88%, respectively.[82] In adults, genetic tests might be particularly helpful in some situations, including patients with a familial history of haemophagocytic lymphohistiocytosis, adult onset of familial haemophagocytic lymphohistiocytosis, history of severe or recurrent EBV infection, patients with recurrent episodes, or individuals without an apparent trigger or underlying predisposing disease.[2,80]

Differential diagnosis

The first diagnostic challenge is to differentiate whether the clinical picture is due to haemophagocytic lymphohistiocytosis or a severe presentation of infection, autoimmune disease, or neoplastic disease associated with haemophagocytic lymphohistiocytosis. In previously healthy people, a clinical picture resembling haemophagocytic lymphohistiocytosis might be seen in presentations of viral primary infections or the onset of neoplastic or autoimmune disease. In patients with underlying disease, a haemophagocytic lymphohistiocytosis-like presentation might be seen in those with severe disease flares (autoimmune disease), rapidly progressive metastases (cancer), or severe acute infections or viral reactivations (immunosuppressed patients). For cases in which hypofibrinogenaemia, hyperferritinaemia, and hypertriglyceridaemia (especially when concentrations are substantially changed) and haemophagocytosis are identified, haemophagocytic lymphohistiocytosis should be regarded as the most probable diagnosis. However, very high ferritinaemia (>22 470 pmol/L) might also be identified in histiocytic malignant diseases and adult-onset Still disease,[2] whereas hypertriglyceridaemia and hypofibrinogenaemia occur in patients with disseminated cancer, sepsis, systemic inflammatory response syndrome, and multiple organ dysfunction syndrome, and haemophagocytosis has been identified in 64% of autopsies of critically ill patients.[83] The clinical presentation of haemophagocytic lymphohistiocytosis often fits into the range of severe complex systemic processes such as septic shock or systemic inflammatory response syndrome and multiple organ dysfunction syndrome,[84,85] which makes differentiation complicated. Additionally, the two most recently introduced haemophagocytic lymphohistiocytosis criteria (high soluble CD25 concentration and decreased NK-cell activity) are also reported in sepsis, systemic inflammatory response syndrome, and multiple organ dysfunction syndrome.[85] Some investigators[85] postulate that sepsis, systemic inflammatory response syndrome, multiple organ dysfunction syndrome, and haemophagocytic lymphohistiocytosis form a disease continuum that might share a common mechanism as their cause—systemic immune dysregulation triggered by a specific external agent.

Supportive treatments

The theoretical basis for treatment of haemophagocytic lymphohistiocytosis requires a triple simultaneous approach. First, support measures are essential because of frequent life-threatening presentation. Second, the elimination of triggers (mainly infection) is crucial to remove the stimuli that initiate abnormal immune system activation. Third, suppression of the inflammatory response and cell proliferation (neoplasia), or both, by immunosuppressive and cytotoxic drugs, respectively, is necessary.

Supportive intensive care guidelines should be similar to standard practice for patients with similar life-threatening diseases such as systemic inflammatory response syndrome or multiple organ dysfunction syndrome; however, specific measures should be added in patients with haemophagocytic lymphohistiocytosis. Hyperinflammation, coagulopathy, and thrombocytopenia put patients with haemophagocytic lymphohistiocytosis at very high risk of spontaneous bleeding; platelet transfusions, fresh frozen plasma and activated factor VII, or both, might be needed for patients with life-threatening acute bleeding.[86–88] Growth factors such as granulocyte colony stimulating factor might be used for severe neutropenia, although isolated reports have associated their administration with exacerbation of haemophagocytic lymphohistiocytosis.[89,90]

Specific treatments

No randomised, controlled clinical trials have investigated potential treatments for haemophagocytic lymphohistiocytosis. All treatment studies in adults have been uncontrolled and retrospective and included less than 20 patients (table 2).[34,91–97] Likewise, most studies have investigated drugs at different doses and in various

combinations. Therefore, treatment decisions continue to be based on clinical experience and expert opinion.

Active infections in a patient with suspected haemophagocytic lymphohistiocytosis should always be treated appropriately. However, supportive care could be as important as the initiation of pathogen-directed treatment, which alone might not be sufficient to control the disease in some patients, especially those with haemophagocytic lymphohistiocytosis related to herpes or influenza virus infections.[41,86] Pathogen-directed treatments seem to be largely used in bacterial infections. In a review[42] of cases of tuberculosis-associated haemophagocytic lymphohistiocytosis, 60–78% of patients given antituberculosis treatment (alone or in combination with immunomodulatory therapy) survived, whereas those not treated died.

Glucocorticoid drugs are predominantly included in initial regimens for the treatment of haemophagocytic lymphohistiocytosis, irrespective of the cause. Efficacy of methylprednisolone pulses as initial monotherapy was reported in nearly half of a cohort of 30 patients with underlying systemic autoimmune diseases.[12] Dexamethasone is the preferred corticosteroid when CNS involvement is suspected, because it crosses the blood–brain barrier better than does prednisone or prednisolone, and is included in the haemophagocytic lymphohistiocytosis 1994 and 2004 protocols.[40,63]

Ciclosporin is the most frequently used immunosuppressive drug in both paediatric and adult patients with haemophagocytic lymphohistiocytosis (appendix p 5), and is associated with a 76% survival rate in patients with autoimmune disease. The 2004 protocol for paediatric patients with haemophagocytic lymphohistiocytosis added ciclosporin as induction therapy,[63] although this use could increase the risk of CNS toxicity due to haemophagocytic lymphohistiocytosis-related liver dysfunction.[98] Therefore, the dose of ciclosporin should be reduced in patients with abnormal liver or renal function. No data are available on the efficacy of other calcineurin inhibitors in adult patients with haemophagocytic lymphohistiocytosis, except for a few cases of efficacy with tacrolimus.[12,99] Other successful immunosuppressive drugs in adult patients with haemophagocytic lymphohistiocytosis include methotrexate in patients with rheumatic diseases and cyclophosphamide in those with systemic autoimmune diseases (appendix p 5). Patients with CNS involvement could be treated with intrathecal methotrexate and hydrocortisone every week, although the risk of posterior reversible encephalopathy syndrome should be considered.[98]

Intravenous immunoglobulin therapy has been successfully used in adults with haemophagocytic lymphohistiocytosis of different causes. Two small series[95,96] of adult patients with haemophagocytic lymphohistiocytosis who were given intravenous immunoglobulins showed promising results, especially patients with infection and autoimmune disease, with an estimated survival rate of 59–75%. The main predictive factor of response was administration within 2 days of the highest ferritin concentrations.[95] Rare reports of renal impairment[100] suggest that renal function should be monitored and nephrotoxic comedication should be avoided.

	N (mean age, years)	Cause of HLH (number)	Study design	Treatment	Survival (%)
Tateishi et al, 2009[91]	8 (ND)	Multiple	Prospective	Continuous haemodiafiltration (PMMA-CHDF) for 3 days	75%
Shin et al, 2008[92]	17 (ND)	ND	Prospective	CHOP	44%
Asci et al, 2006[93]	6 (ND)	Kidney transplant	Retrospective	High-dose IVIG	100%
Imashuku et al, 2003[94]	10 (23)	Infection	Retrospective	HLH-94 protocol (4), etoposide (4)	75%, 0%
Emmenegger et al, 2001[95]	20 (42)	Autoimmune disease (12), infection (3), idiopathic (5)	Retrospective	IVIG, ranging between 0·3 g/kg and 1 g/kg per bodyweight for 1–5 days	75%
Larroche et al, 2000[96]	17 (ND)	Infection (9), other (8)	Multicentre, retrospective	High-dose IVIG (mean 1·6 g/kg per bodyweight for 3 days)	59%
Tsuda et al, 1997[97]	7 (55)	EBV (3), cytomegalovirus (1), tuberculosis (1), idiopathic (2)	Retrospective	Ciclosporin A 200–250 mg/day (plus G-CSF in 5 patients)	86%
Ahn et al, 2010[34]	16 (47)	EBV	Retrospective	Conservative Corticosteroids Corticosteroids + IVIG Corticosteroids + IVIG + etoposide Corticosteroids + IVIG + etoposide + ciclosporin A	0% 50% 100% 11% 50%
Ahn et al, 2010[34]	6 (42)	Idiopathic	Retrospective	Conservative Corticosteroids +IVIG Corticosteroids + IVIG + etoposide Corticosteroids + IVIG + etoposide + cyclosporine A Alemtuzumab-CHOP	100% 100% 50% 100% 100%

HLH=haemophagocytic lymphohistiocytosis. ND=not detailed. PMMA-CHDF=polymethyl methacrylate membrane haemofiltre. CHOP=cyclophosphamide, adriamycin, vincristine, and prednisone. IVIG=intravenous immunoglobulin. EBV=Epstein-Barr virus. G-CSF=granulocyte-colony stimulating factor.

Table 2: **Summary of the main characteristics of therapeutic studies in adults with HLH[91-98]**

Case reports and small series have shown a survival rate of nearly 80% in patients with cancer, infection, and autoimmune disease who are treated with plasma exchange (appendix p 5).

1994 and 2004 guidelines for haemophagocytic lymphohistiocytosis[40,63] include specific chemotherapy as the key therapeutic approach for paediatric disease. The 1994 protocol included an 8-week induction therapy with dexamethasone, etoposide, and intrathecal methotrexate, and showed increased survival compared with historical controls. However, no studies have investigated the efficacy of these protocols in adults, although a global analysis of adult case reports shows that therapeutic regimens containing etoposide are associated with better survival in patients with cancer and infection (71–75%) than in those with autoimmune diseases (57%) (appendix p 5). Because the mortality rate was 14-times higher in children with EBV-associated haemophagocytic lymphohistiocytosis who were not given etoposide within the first 4 weeks,[101] and it has been suggested that etoposide might act by partly blocking EBV,[102] etoposide might be an option in refractory or severe adult cases of EBV-related haemophagocytic lymphohistiocytosis. Because etoposide is cleared by the liver and kidneys, the dose should be reduced in patients with renal or liver failure, and haemopoietic cell transplantation should be done as soon as possible because of the high risk of infection, disease reactivation, and secondary malignancies associated with prolonged etoposide use.

There are few reports of the successful use of biological treatments for adults with refractory haemophagocytic lymphohistiocytosis. These treatments included rituximab, infliximab, and etanercept, after patients did not respond to ciclosporin and intravenous immunoglobulin, or etoposide, or both.[12,103,104] Evidence supporting these recommendations is scarce, but common sense and consideration of the underlying disease might help to select the most appropriate biological drug. Thus, the use of anti-TNF drugs for patients with haemophagocytic lymphohistiocytosis and rheumatoid arthritis or spondyloarthropathies, anti-interleukin 1r (anakinra) and interleukin-6 (tocilizumab) for patients with adult-onset Still's disease, and B-cell depleting drugs (rituximab, belimumab) for those with systemic lupus erythematosus, Sjögren's syndrome, or antineutrophil cytoplasmic antibody-associated vasculitides might be proposed. In patients with EBV-related haemophagocytic lymphohistiocytosis with or without associated lymphoma, rituximab might be a salvage treatment option.[30,105–109]

Follow-up and patient outcome

Close clinical and biological follow-up is essential during the first weeks of treatment because absence of response at 2–3 weeks is often a sign of refractory haemophagocytic lymphohistiocytosis. C-reactive protein concentration and erythrocyte sedimentation rate might be useful to monitor disease activity and assess intercurrent bacterial infection or therapeutic response. Some studies[30,110] have suggested an association between the therapeutic response and a rapid reduction in laboratory parameters such as hypertriglyceridaemia or hyperferritinaemia, whereas in patients with EBV-related haemophagocytic lymphohistiocytosis, quantitative analysis of the cell-free EBV genome copy number 4 months after therapy might help assess the response to treatment and have prognostic value.[70] Unfortunately, there is little evidence for the management of refractory haemophagocytic lymphohistiocytosis in adults; however, isolated cases suggest successful use of ciclosporin after patients did not respond to intravenous immunoglobulin,[111–113] tacrolimus after no response to ciclosporin,[112] and etoposide after no response to ciclosporin or intravenous immunoglobulin.[114,115]

Relapse of haemophagocytic lymphohistiocytosis after a good therapeutic response is not infrequent, although the rate and possible associated risk factors are unknown. Any new episode of fever should be carefully assessed for possible reactivation. Some investigators[116] suggest that a decrease in haematological or liver signs with steady or increased concentration of serum ferritin, soluble CD25, and soluble CD163 might suggest a possible relapse. Relapse can occur when initial treatment is tapered or withdrawn; patients in relapse often respond to restoration (or reintensification of ongoing therapy) during the induction.

Prognostically, haemophagocytic lymphohistiocytosis is one of the most critical clinical disorders in adults; the mortality rate was 41% in 1109 adults.[4,12–17,19,32,34,36,37,39] The underlying causes strongly affect survival, with a poor outcome in patients with neoplasia (especially NK or T-cell lymphoma) and better results associated with primary viral infection and autoimmune diseases (appendix p 6). Appendix p 7 summarises the main prognostic factors identified in studies of adult patients with haemophagocytic lymphohistiocytosis. A high mean age at diagnosis and thrombocytopenia are the prognostic factors most frequently associated with death, whereas patients with haemophagocytic lymphohistiocytosis and underlying neoplasia or idiopathic causes have a poor outcome compared with patients with other causes of the disease. Some investigators suggest that low glycosylated ferritin concentration could be a marker of severe haemophagocytic lymphohistiocytosis,[2] whereas others have associated the rate of decrease in ferritin concentration with mortality in children.[110]

Although the mortality rate is high during the first weeks of disease due to progressive multiple organ failure, later mortality, mainly due to drug toxicities and infections in patients with persistent neutropenia, can occur. Additionally, a close follow-up is mandatory in adult patients who have survived idiopathic haemophagocytic lymphohistiocytosis, because a further diagnosis of haematological neoplasia in some cases after a mean of 5–16 weeks.[117,118] A second haematological neoplasia has

been reported in some patients diagnosed with haemophagocytic lymphohistiocytosis-related lymphoma.[119,120]

Future perspectives

The very broad pathogenic scenario of haemophagocytic lymphohistiocytosis, in which genetic defects, predisposing diseases, and triggers of different causes are mixed together with the high mortality rate, makes the disease one of the most complicated disorders. Although most efforts have focused on investigation of the disease in children, this tendency has changed in recent years and various studies are trying to shed light on adult haemophagocytic lymphohistiocytosis.

Risma and Jordan[121] have postulated an age-related decreasing genetic susceptibility pattern, in which truncating mutations seem to present at early ages, whereas hypomorphic mutations (missense or splice site, or both) present at older ages. Zhang and colleagues[122] identified mutations in 25 (14%) of 175 adult patients; nearly half having the A91V-PRF1 genotype. Some adults with hypomorphic mutations might only develop haemophagocytic lymphohistiocytosis when there is a combination of various triggers and predisposing disorders.

One of the least understood aspects in the clinical approach to the disease is the absence of standardised diagnostic criteria that are adapted to adults, resulting in frequent missed or delayed diagnoses, even though Emmenegger and coworkers[2] proposed a diagnostic algorithm a few years ago. The diagnostic guidelines proposed by the Histiocyte Society[3,63] are mainly based on clinical experience in children, but are widely used in adults, even though no studies have analysed their sensitivity and specificity, especially in the differentiation of haemophagocytic lymphohistiocytosis from other systemic inflammatory processes (sepsis, cancer, and adult-onset Still's disease). Furthermore, there is no information about the value of the two last criteria added or why five of eight criteria are needed to reach the diagnosis. Isolated studies in adults have calculated the sensitivity and specificity of some diagnostic tests, such as histopathological haemophagocytosis (80–83% and 60%, respectively),[79,123] high ferritin concentrations (77–82% and 43%, respectively),[124,125] and combined high concentrations of ferritin and soluble interleukin 2 receptor (positive predictive value of 96%).[126] An international, multidisciplinary effort to develop specific criteria for adults is needed.

Genetic and immunological studies might lead to advances in the diagnosis and treatment of adult haemophagocytic lymphohistiocytosis. Sumegi and colleagues[127] reported the potential use of gene-expression signatures to classify the disease. Xu and colleagues[128] reported a differentiated interferon γ blood cytokine profile in adult cases of haemophagocytic lymphohistiocytosis compared with with other life-threatening inflammatory states, which supported the dominant role of interferon γ identified in animal models, whereas Lykens and colleagues[53] suggested that the key pathogenic finding is excess of acutely activated T cells. These studies suggest that therapies targeting interferon γ and T cells might benefit patients with haemophagocytic lymphohistiocytosis. Alemtuzumab has been used in three adult patients with haemophagocytic lymphohistiocytosis, which led to variable outcomes,[129–131] but might have a role as a salvage treatment before haemopoietic cell transplantation therapy in refractory patients.[132] Unfortunately, case control studies and, therefore, clinical trials, are difficult to design for haemophagocytic lymphohistiocytosis.

Conclusion

Haemophagocytic lymphohistiocytosis is an increasingly recognised disorder in adults. It has a life-threatening clinical presentation that affects a wide range of organ systems. Haemophagocytic lymphohistiocytosis manifests in patients with a range of underlying diseases but, unlike in children where the study of haemophagocytic lymphohistiocytosis is led by paediatricians, in adults many medical specialties are involved. We show that there is little evidence for adult haemophagocytic lymphohistiocytosis, especially with respect to the diagnosis and therapeutic approaches. The body of evidence relies predominantly on case series and uncontrolled studies. Therefore, diagnostic and therapeutic decision-making continues to be on the basis of clinical experience and expert opinion. An increased understanding of the causes of adult haemophagocytic lymphohistiocytosis, active multidisciplinary collaboration promoting international multicentre registries and clinical guidelines, and the development of more-specific therapies, could help to improve the poor outcome of haemophagocytic lymphohistiocytosis.

Contributors

MR-C, PB-Z, and XB conceived and designed the Seminar, MR-C, PB-Z, AL-G, MAK, and XB gathered the data, MR-C, PB-Z, AL-G, MAK, and XB analysed and interpreted the data, MR-C, PB-Z, and XB drafted the Seminar, and MR-C, PB-Z, AL-G, MAK, and XB revised the Seminar for important intellectual content.

Conflicts of interest

We declare that we have no conflicts of interest relevant to the content of this Seminar.

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