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REVIEW

Viral infections associated with haemophagocytic syndrome

Nadine Rouphael Maakaroun[1][*][†], Abeer Moanna[2][†], Jesse T Jacob[1][†]
and Helmut Albrecht[3][‡]

[1]*Division of Infectious Diseases, Emory University School of Medicine, Atlanta, GA 30303, USA*
[2]*Division of Infectious Diseases, Emory University School of Medicine, Veterans Affairs Medical Center, Decatur, GA 30033, USA*
[3]*Division of Infectious Diseases, University of South Carolina, Columbia, SC 29203 USA*

SUMMARY

Haemophagocytic syndrome (HPS) or haemophagocytic lymphohistiocytosis (HLH) is a rare disease caused by a dysfunction of cytotoxic T cells and NK cells. This T cell/NK cell dysregulation causes an aberrant cytokine release, resulting in proliferation/activation of histiocytes with subsequent haemophagocytosis. Histiocytic infiltration of the reticuloendothelial system results in hepatomegaly, splenomegaly, lymphadenopathy and pancytopenia ultimately leading to multiple organ dysfunctions. Common clinical features include high fevers despite broad spectrum anti-microbials, maculopapular rash, neurological symptoms, coagulopathy and abnormal liver function tests. Haemophagocytic syndrome can be either primary, i.e. due to an underlying genetic defect or secondary, associated with malignancies, autoimmune diseases (also called macrophage activation syndrome) or infections. Infectious triggers are most commonly due to viral infections mainly of the herpes group, with EBV being the most common cause. HPS can be fatal if untreated. Early recognition of the clinical presentation and laboratory abnormalities associated with HPS and prompt initiation of treatment can be life saving. HPS triggered by viral infections generally does not respond to specific antiviral therapy but may be treated with immunosuppressive/immunomodulatory agents and, in refractory cases, with bone marrow transplantation. Copyright © 2010 John Wiley & Sons, Ltd.

DEFINITION, EPIDEMIOLOGY AND CLASSIFICATION

Haemophagocytic syndrome (HPS), also called haemophagocytic lymphohistiocytosis (HLH) [1],

Corresponding author: N. Rouphael Maakaroun, Division of Infectious Diseases, Emory University School of Medicine, 80 Butler Street, Atlanta, GA 30303, USA. E-mail: nroupha@emory.edu
[†]*Assistant Professor.*
[‡]*Professor of Medicine, Division Chief.*

Abbreviations used

BMT, bone marrow transplantation; CMV-AHS, CMV associated HPS; CTLs, cytotoxic T cells; EBV-HLH, EBV associated HLH; EBV-HPS, EBV associated HPS; FHLH, familial form of HLH; HAART, highly active antiretroviral therapy; HAV-HPS, hepatitis A associated HPS; HLH, haemophagocytic lymphohistiocytosis; HPS, haemophagocytic syndrome; HSCT, haematopoietic stem cell transplantation; IAHS, infection associated HLH; IM, infectious mononucleosis; IAHS, infection associated HLH; IRIS, immune reconstitution inflammatory syndromes; IVIG, Intravenous gamma immunoglobulins; LAHS, lymphoma-associated haemophagocytic syndrome; MAS, macrophage activation syndrome; M-CSF, macrophage-colony-stimulating factor; T/NK, T and natural killer; sCD25, alpha chain of the IL-2 receptor; VAHS, virus–associated HPS; XLP, X-linked lymphoproliferative syndrome

is characterised by impaired or absent activity of NK cells and cytotoxic T-cells leading to cytokine dysregulation with proliferation and activation of histiocytes. HPS results in multiorgan dysfunction and haemophagocytosis within the reticuloendothelial system characterised by pancytopenia and organomegaly [1]. If untreated, HPS can be fatal. HPS was first described by Scott and Robb-Smith in 1939 [2] who termed it 'histiocytic medullary reticulosis'. Virus–associated HPS (VAHS) was first characterised in 1979 by Risdall in a case series of 19 patients [3].

The incidence of HPS is difficult to estimate since the syndrome is certainly underdiagnosed. A nationwide survey of HPS in Japan, where a large number of HPS studies have been done, reported [4] an annual incidence of 1 in 800 000.

HPS can be divided into primary or genetic HPS and secondary or reactive HPS (Table 1). Primary HPS usually occurs early in life and is associated

Table 1. Classification of HPS

Primary or genetic	Familial form
	Forms associated with immune deficiency syndromes
Secondary or reactive	Macrophage activation syndrome (MAS) associated with autoimmune diseases
	Malignancy associated HLH (especially lymphoma-associated hemophagocytic syndrome(LAHS)
	Infection associated HLH (IAHS)

with a higher mortality rate, while secondary HPS occurs later in life and generally carries a better prognosis. This distinction is not categorical as primary HPS can occur later in life [5], may be triggered by infections, [6] and may not be associated (up to 50–60% [7]) with a 'typical' genetic mutation.

Genetic HPS

The familial form of HLH (FHLH) was first described in 1952 [8] by Farquhar and Claireaux. FHLH is an autosomal recessive disorder estimated to occur in 1 out of 30 000 to 50 000 births [9,10] and in 70–80% of cases manifests in the first year of life. Other forms of genetic HPS are associated with immune deficiency syndromes including Chediak–Higashi syndrome, Griscelli syndrome, X-linked lymphoproliferative syndrome (XLP), Wiskott–Aldrich syndrome, severe combined immunodeficiency, lysinuric protein intolerance and Hermansky–Pudlak syndrome.

Reactive HPS

The true incidence of reactive HPS is difficult to define. Reactive HPS can be divided into three categories:

1. *Macrophage activation syndrome* [11] associated with autoimmune diseases.
2. *Malignancy associated HLH* [12] (especially lymphoma-associated haemophagocytic syndrome).
3. *Infection associated HLH* [13] (*IAHS*).

IAHS are most commonly associated with viral infections, which are the focus of this review. IAHS can also be caused by bacterial infections including mycobacteria and spirochetes as well as fungal and parasitic pathogens [1]. A review of the published cases in 219 children diagnosed with IAHS before 1996 [12] found that more than half were from the Far East. EBV was the triggering virus in 74% of the children in whom an infectious agent was identified. Overall mortality was 52% but was higher (73%) in patients with EBV–HPS.

PATHOPHYSIOLOGY

Haemophagocytic disorders arise from defects in critical regulatory pathways responsible for the natural termination of immune and inflammatory responses with a subsequent failure of a homeostatic removal of cells that are superfluous or dangerous to the host organism. The role of granule (perforin/granzymes)-mediated cytotoxicity is important in both the killing of infected cells and the termination of the immune response [14]. Genetic HPS can be attributed to a defect in the mechanism of granule (perforin/granzymes)-mediated cytotoxicity. Several genetic loci related to the activity of perforin/granzymes granules have been implicated in the pathophysiology of genetic HPS [15]. A defective triggering of apoptosis in FHLH has also been described in reference [16]. Specific genes or mutations associated with primary HPS include the PRF1 gene (perforin), the Munc 13-4 family of genes, the syntaxin 11 gene and the SH2-domain containing gene 1A.

The pathophysiology of acquired HPS is not fully understood. It certainly involves the interaction between T cells and macrophages but this does not exclude a genetic predisposition in affected cases.

The persistent activation of lymphocytes is the result of an uncontrolled immune response causing a hypersecretion of pro-inflammatory cytokines such as IFNγ [17], TNFα [18], IL-6 [19], IL-8, IL-10 [18], IL-16 [20], IL-18 [21] and macrophage-colony-stimulating factor (M-CSF). IL-18 appears to play a crucial role particularly in autoimmune related HPS. In addition, higher levels of IFNγ and IL-10 are associated with a worse prognosis in childhood HPS [22]. The activation of T lymphocytes also results in an elevation of soluble IL-2 receptor [23] which is one of the diagnostic criteria of HPS and correlates with prognosis [24]. Furthermore, the presence of a specific TNFα polymorphism has been associated with

an increased susceptibly to reactive HPS in certain Asian populations [25].

The proliferation of histiocytes is characterised by an up-regulation of adhesion and MHC Class I and II molecules [26] on monocytes/macrophages and expansion of inflammatory monocytes (increase in CD14/CD16 expression [27]).

The persistent activation of lymphocytes [28] and proliferation of histiocytes leads to organ infiltration and hemophagocytosis of various blood cells by macrophages present in bone marrow, lymph nodes and spleen.

CLINICAL PRESENTATION AND DIAGNOSIS

Diagnosis of HPS relies on specific clinical, laboratory, and histopathological findings proposed by the Histiocyte Society in 1991 [29] and updated in 2004 [30] (Table 2).

The main symptoms and signs of HPS are prolonged high fever, splenomegaly and cytopenias involving more than two cell lines. Less frequently observed clinical findings include jaundice, hepatomegaly, lymphadenopathy, rash and neurological signs (Table 3). Common laboratory findings result from prominent liver dysfunction [31]: low fibrinogen levels, high bilirubin levels, elevated serum transaminases, elevated prothrombin and partial thromboplastin times. High triglyceride levels are common in HPS and are therefore included in the diagnostic criteria. In a study of 28 patients with secondary HPS, 68% had hypertrigyceridemia at diagnosis or at some time during the disease process and triglyceride levels subsequently decreased with successful treatment of

Table 3. Common clinical manifestations of HPS (from the most frequent to the less frequent)

Fever
Splenomegaly
Hepatomegaly
Neurologic Manifestations
Lymphadenopathy
Skin Rash

HPS [32]. An often striking elevation of ferritin [33] levels is characteristic though it can be found in other diseases. A study from Texas found that a ferritin level above $10\,000\,\mu g/L$ was 90% sensitive and 96% specific for HPS [34]. Two other main diagnostic parameters are an increased plasma concentration of the alpha chain of the IL-2 receptor (sCD25) and impaired NK cell activity.

Typical histopathologic findings include activated macrophages with engulfed leukocytes, erythrocytes, platelets and their precursor cells. The haemophagocytosis can be seen in any organ but is particularly common in bone marrow, lymph nodes, liver and spleen eventually resulting in organomegaly and organ failure. At presentation, hemophagocytosis is only found in a minority of cases, but can be more easily detected as the syndrome progresses. Therefore, if haemophagocytosis is absent in initial biopsy specimens, the biopsy may need to be repeated in cases with high suspicion.

Table 2. Diagnostic guidelines for hemophagocytic syndrome (HLH-04)

The diagnosis of HPS is established if one or two of the following criteria are fulfilled:
  (1) A molecular diagnosis consistent with HPS (i.e., PRF mutations, SAP mutations, MUNC13-4 mutations)
  (2) Five out of eight of the following criteria
      Clinical = Fever
             Splenomegaly
      Laboratory = Cytopenia (affecting > 2 cell lineages, hemoglobin $\leq 9\,g/dl$, platelets $< 100\,000/\mu l$, neutrophils $< 1000/\mu l$)
             Elevated triglyceride levels ($\geq 265\,mg/dl$) and/or low fibrinogen levels ($\leq 150\,mg/dl$)
             Elevated ferritin levels (($\geq 500\,ng/ml$)*
      Histopathology = Hemophagocytosis without evidence of malignancy
      Biologic markers = Low or absent NK cell cytotoxicity*
             Elevated soluble CD25 (IL-2Rα chain; $\geq 2400U/ml$)*

*Criteria added to the previous HLH diagnostic guidelines.

Once a diagnosis of HPS is established, a search for an underlying disease (genetic, rheumatologic or malignant disease) and a possible infectious trigger should be performed.

TREATMENT

HPS is frequently fatal if not treated promptly. As early therapy for HPS can be life saving and some of the diagnostic criteria may only become apparent late in disease it is not necessary to fulfil all diagnostic criteria before initiating therapy.

Treatment is based on the control of the cytokine storm and the cellular proliferation. In IAHS, treatment of the underlying infectious trigger is not sufficient to control the disease especially if HPS is associated with EBV. Immunochemotherapy as proposed by the Histiocyte Society (with the HLH-94 protocol [35,36] and subsequently the HLH-04 protocol [30]) consists of combination therapy with etoposide, dexamethasone and cyclosporine A as well as, in selected patients, intrathecal therapy with methotrexate and corticosteroids. The HLH-94 protocol was found to be highly effective in an early series of 17 cases of EBV–HPS [37]. The efficacy of HLH-94 was later confirmed by a large series including 47 patients of EBV–HPS [38] where none of the 33 patients receiving more than four doses of etoposide died. The prompt use of etoposide (less than 4 weeks after diagnosis) greatly improves the outcome in both pediatric [38] and adult patients [39]. The use of cyclosporine in treating HPS was first suggested by Oyama *et al.*, in 1989 [40] when it was found to reduce the rate of fatal infections associated with neutropenia.

Although these immunemodulating chemotherapies are effective, they are commonly associated with side effects, most of which are more pronounced following prolonged courses of treatment. Cyclosporine is associated with severe headaches, hypertension, seizures and renal impairment. Corticosteroids have many well-described adverse effects, including hyperglycemia, fluid retention, hypertension and weight gain. Etoposide is associated with myelosuppression and development of secondary leukemia.

Intravenous gamma immunoglobulins (IVIG) [41] used with or without corticosteroids to treat HPS are usually not effective as monotherapy. Seventeen out of 21 patients treated with IVIG ± corticosteroids had to be switched to an etoposide-based regimen to better control the disease [38]. The 4 year survival was 68% for the IVIG(corticosteroids group, compared to 86% for the group that received an etoposide containing regimen as first line therapy. The use of growth factors such as granulocyte (G)-CSF or granulocyte monocyte (GM)-CSF is generally not recommended as they can exacerbate HPS [42].

Haematopoietic stem cell transplantation (HSCT) is recommended for patients with genetic forms and for patients with recurrent, persistent or refractory severe disease. HSCT has greatly improved the survival of FHLH. A retrospective review of FHLH 25 years ago [43] described a mean survival of less than a month after onset of symptoms and a 1 year overall survival of less than 5%. Currently, definitive treatment and potential cure of FHLH is only achieved by HSCT with projected 5 year survival rates [44] ranging from 50% to 70%. In 1996, Arico *et al.* [45] reviewed 122 patients with FHLH. Bone marrow transplantation (BMT) recipients had a significantly superior outcome in comparison with non-transplanted patients with a 66% versus 10.1% survival rate. Combining both, chemotherapy and BMT treated patients; the probability of survival at 3 years was 55% for all cases.

VIRAL INFECTIONS ASSOCIATED WITH HPS

EBV

Epidemiology

Epstein-Barr virus (EBV) is a ubiquitous herpesvirus associated with most cases of infection associated HPS [46]. The epidemiology of EBV associated HPS/HLH (EBV–HPS or EBV–HLH) is not well known. EBV–HPS has a higher incidence in Asian countries where each year in Japan, 25 cases of EBV HPS are diagnosed with female predominance and a peak incidence between 1 and 2 years of age [47]. The higher incidence rates in Asian countries are theorised to be due to a more pathogenic viral strain of EBV [48] genetically similar to viral strains obtained from nasopharyngeal carcinoma cell lines. EBV–HPS has been described in Western countries and the prevalence in non-Asian populations may be underestimated [49–51]. Information on the epidemiology of EBV–HPS in adults is lacking.

Pathophysiology

Primary EBV infection is usually asymptomatic expect for infectious mononucleosis [52] (IM), seen commonly in children and young adults. During primary infection, EBV typically infects and replicates in B cells. After primary infection, EBV-specific T cells (cytotoxic T cells or CTLs) are usually acquired to regulate EBV-infected B cells and induce memory B cells. While EBV has a well-described tropism for B cells and nasopharyngeal epithelial cells, the invasion of non-B cell populations plays an important role in the pathogenesis of several severe EBV related diseases, with disease manifestations generally depending on the type of EBV-infected cell [53] and the state of the host immunity. In rare cases, for instance, EBV infects T and natural killer (T/NK) cells and can induce persistent EBV infection in these cells. Refractory and severe EBV disease results from either (i) chronic active EBV infection [54] (ii) acute fulminant EBV HPS [55] (iii) lymphoproliferative disorders (T/NK cell leukemia/lymphoma [56] or lymphoma associated haemophagocytic syndrome [57]). In chronic EBV infection, primarily CD4+ T cells or NK cells are affected. A dysfunction in T/NK cells results in a decrease in EBV-specific CTLs and subsequent EBV-associated T/NK cell lymphoproliferative disease. In EBV–HPS, EBV infects primarily CD8+ cells [58] and results in a cytokine storm with the release of proinflammatory and Th1-type cytokines [59] including TNFα and IFNγ, resulting in the secondary activation of histiocytes and macrophages [53]. The cytokine response seen in EBV–HPS tends to be much more pronounced than the one observed in non-EBV–HPS [60].

Although EBV–HPS probably develops as a result of some element of immune dysfunction, the precise characteristics of host vulnerability to EBV are largely unknown, and the majority of EBV–HPS cases occur in apparently immunocompetent and previously healthy children, adolescents and young adults. Cases of EBV–HPS can also be seen in the setting of established immune deficiencies such as FHLH [43] and XLP [61].

Diagnosis [62]

Serological testing can help to determine if the EBV–HPS occurred in the setting of primary infection or is the result of a reactivation process. In a recent epidemiological study from Japan, the vast majority of EBV–HPS cases occurred in children with primary infection. Reactivation was considered a risk factor for worse outcome [4]. However, serologic methods carry some limitations. Real-time PCR allows the quantitative measurement of EBV viral load. Even though the vast majority of EBV in peripheral blood is found within leukocytes, EBV PCR of whole blood and serum are considered to adequately reflect the EBV load in terms of viral replication [63]. EBV PCR levels in EBV–HPS are usually higher than those seen in EBV-IM [64]. EBV viral load is considered a prognostic factor and a measure of the efficacy of treatment [65] in EBV–HPS.

Various cell sorting techniques can be used to determine if T cells or NK cells are primarily involved and to confirm the diagnosis [50]. Clonality should be determined by cytogenetic analysis, T-cell receptor gene rearrangements, or Southern blot analysis for fused termini of the EBV genome, utilising blood, bone marrow or other lymphoid tissues.

Genetic testing for inherited conditions linked to hemophagocytosis, such as familial HLH and XLP should be considered, particularly in young (< 1 year of age) or male patients with EBV–HPS, when there is consanguinity between parents, when HPS is present in another sibling, or when HPS is relapsing or refractory.

Treatment

Mild cases of EBV–HPS are treated conservatively since spontaneous regression of EBV–HPS has been described in reference [66]. Antiviral therapy with acyclovir, ganciclovir or cidofovir is generally ineffective in IM and has provided disappointing results in EBV–HPS.

The optimal treatment strategy [67] for EBV–HPS consists of:

(i) Control of the cytokine storm resulting in multiorgan failure and coagulopathy. Antithymocyte globulins [68], splenectomy [69] and plasma exchange or blood exchange transfusion [70] have been used in the treatment of EBV–HPS.
(ii) Control of opportunistic infections particularly fungal and bacterial [71] infections in the setting of neutropenia.
(iii) Eradication of proliferating clonal and EBV containing T cells and NK cells. Immunosup-

pressive medications inhibiting overactive T and NK cell responses, in conjunction with chemotherapeutic agents targeting dividing lymphocytes and mononuclear phagocytes are typically used to treat EBV–HPS. Early treatment is associated with markedly improved survival [47]. Addition of agents that eliminate EBV infected B cells may decrease EBV viral loads and improve the efficacy of current therapeutic arsenal but are ineffective alone. Rituximab [72], a humanised anti-CD20 monoclonal antibody that targets mature B cells, was added to standard regimens to treat a few cases of EBV–HPS [73].

HSCT or BMT has become the treatment of choice for HLH as well as refractory cases of EBV–HPS [74]. EBV–HPS carries the worst prognosis among viral infections associated with HPS. However, with the use of HLH-94 and HLH-04 protocols and, if necessary, BMT, the prognosis of EBV–HPS has improved dramatically. In 78 patients with EBV–HPS treated between 1992 and 2001, 75.6% were alive following a median follow-up of 43 months [75]. 85% of these patients were treated with etoposide-based regimens, 15% with BMT. 20% experienced a relapse.

OTHER HERPESVIRUSES
Aside from EBV, the most common herpesviruses associated with HPS are CMV and HHV8.

CMV infection has been associated with HPS (CMV–AHS) in different settings. It has been observed in healthy patients [76,77], premature infants [78], patients with inflammatory bowel disease [79,80], rheumatological diseases [81,82], cancer [83] and in transplant recipients [84,85]. In a prospective study of 171 patients undergoing HSCT, 7 (4%) developed HPS with CMV being the most common trigger in 3 cases [86]. The use of CMV hyperimmune globulin, foscarnet or ganciclovir has been associated with recovery in selected cases [77,79–81,85]. Younger age may be associated with a worse prognosis, with fatal outcomes occurring in four of the five infants in the HLH Japanese registry with CMV–AHS diagnosed at less than a year old [87] (1986–2002).

HHV-8 has been associated with HPS, mostly in the setting of Kaposi's sarcoma [88], multicentric Castleman's disease [89] or lymphoproliferative disorder [90], in immunocompromised hosts

(HIV [91], transplant [92]) and rarely in immunocompetent hosts [93,94]. In a prospective cohort of 44 patients with Castleman's disease and HIV, 4 (9%) had HPS [89]. Interestingly, in this series the cytokine levels of many known inflammatory markers were not elevated; however, IL-8 and IFNγ were increased. In this study, all patients recovered after treatment with splenectomy, etoposide and rituximab [95] based regimens. Ganciclovir and foscarnet have also been associated with recovery in some HHV8–HPS cases.

All other herpesviruses [96–99] with the exception of HHV-7 have been associated with HPS.

HIV
HPS associated with HIV [100] infection is seen in several different settings. Cases have been reported in acute or late HIV infection, in conjunction with immune reconstitution inflammatory syndromes (IRIS), in the setting of infections (both opportunistic and non opportunistic) [101] or malignancies.

Even though hemophagocytosis was observed in 20% of 56 autopsy cases of HIV positive patients [102], clinically apparent HPS is rare in this setting. This association, however, may be underreported and underdiagnosed since HIV and HPS share many similar clinical and biological findings.

To the best of our knowledge, 9 cases of acute HIV with HPS have been reported in the literature [103–105]. There was a male predominance (M:F = 8:1) with a median age at onset of 27. Almost two thirds had a CD4 count < 200 cells/μl with a range of 63–500 cells/μl. Treatment consisted mainly of IVIG ($n = 3$) and steroids ($n = 2$); highly active antiretroviral therapy (HAART) [104,105] was only initiated during the acute phase in 2 cases. All cases reported in the literature survived.

In a review of 39 HIV–HPS cases [106] by Bhatia and colleagues, 82% were male with a median age of 38 years (range 26–59). 80% had a CD4 less than 200 cells/μl with a mean of 132 cells/μl. A lower CD4 count was associated with a worse prognosis. Eleven patients had no opportunistic infection or malignancy suggesting a possible pathogenetic role of HIV itself. Most of the patients presented with fever, two thirds had hepatomegaly and more than half had splenomegaly; pancytopenia was very common. When information was available ($n = 15$) regarding treatment, only three received HAART and only one responded [107]

to HAART. Two received chemotherapy inconsistent with the HLH protocol, six received IVIG, five received corticosteroids and two underwent splenectomy. Overall, recovery was noted in only 28% of patients with half of the deaths occurring within 1 month following the diagnosis of HPS.

Four cases of HIV–AHS have been described in the setting of IRIS [108–110]. All patients were male and reported ages ranged from 33 to 45 years. Symptoms occurred within 1 to 3 weeks following initiation of HAART. IRIS HIV–HPS has occurred in the setting of histoplasmosis [110] as well as Hodgkin's lymphoma [109]. Both patients with Hodgkin's lymphoma were treated with chemotherapy [109] and one of them survived. The patient with histoplasmosis survived following treatment with IVIG and amphotericin [110]. The fourth patient had a fatal outcome despite treatment with etoposide and corticosteroids [108].

INFLUENZA

The association of HPS with influenza has been described in both immunocompromised [111–114] and in immunocompetent patients [115,116]. In a prospective pediatric study [117], one fatal case of HPS was observed among 32 children hospitalised with seasonal influenza. Influenza associated HPS has been seen with seasonal [111–117], avian [118,119] and swine (non-pandemic) influenza [120].

Patients with severe H5N1 (avian) influenza infection have symptoms and laboratory findings similar to those seen in HPS, mainly encephalitis [121], organ dysfunction with haemophagocytosis [122], bone marrow failure [122,123] and cytokine storm [124,125]. Haemophagocytosis seen on autopsy and biopsy is the most common characteristic pathological finding [119,125,126]. The haemagglutinin found in H5N1 viruses may suppress perforin expression and reduce cytotoxicity of human CD8+ T cells including their ability to kill H5-bearing cells leading to marked lymphoproliferation and IFN-γ hyperproduction with macrophage overactivation [127]. With some viruses being resistant to amantadine [128,129] and less commonly, even to certain neuraminidase inhibitors [130,131] and since many similarities exist between HPS and severe flu infection, some authors have speculated that the use of a modified HLH-94 protocol [132] with shorter course of etoposide and dexamethasone should be considered in H5N1 infections associated with HPS.

One fatal case of swine flu associated HPS in an immunocompetent patient has been reported in 1998 [120]. While it is possible that some fatal cases of the novel (swine-origin) H1N1 pandemic strain could also be due to HPS, it is currently unclear how much HPS contributes to the pathology of severe novel H1N1infection.

PARVOVIRUS

Approximately 30 cases [70,133–139] of parvovirus B19 infection have been associated with HPS. The most common underlying disease was hereditary spherocytosis. More than half of the patients were female and most of the cases were seen in adolescents and adults. The majority of patients with parvovirus-associated HPS survived without any specific therapy suggesting that parvovirus-associated HPS carries a better prognosis than other VAHS.

VIRAL HEPATITIS

Fulminant viral hepatitis may mimic but can also be a cause of a true HPS. Hepatitis A virus is more commonly associated with HPS than the other hepatitis virus including hepatitis B or hepatitis C. Fifteen cases [140–142] of HAV–HPS have been described in the literature; all except 4 cases were reported from Asia. The age range was 3–49 years with a median age of 28 and no gender predilection was noted. Three patients had concurrent rheumatologic diseases (systemic juvenile idiopathic arthritis, Still's disease), two patients also had hepatitis C and one patient was an alcoholic. Four patients received no specific treatment but survived. Most commonly, treatment consisted of corticosteroids ± IVIG. Eleven out of the 15 cases had a favourable outcome.

OTHER VIRUSES

There are 12 cases of enterovirus-associated HPS that have been described in the English literature [143]: 5 cases occurred in infants less than 1 year of age, the oldest patient were 18 years old. Underlying diseases were found in 4 cases (Hodgkin's lymphoma, non–Hodgkin's lymphoma, acute lymphoblastic leukemia and juvenile arthritis) and was associated with a higher fatality rate (75%). Ten patients received IVIG, six in combination with steroids. Overall, seven patients survived.

Other viruses found to be associated with HPS include: adenovirus, BK virus, measles, mumps, rubella, parainfluenza virus, dengue, hantavirus, hemorrhagic fever and severe acute respiratory syndrome associated coronavirus [1].

CONCLUSION

Haemophagocytic syndrome is a rare, often fatal disease frequently triggered by viral infections, most notably EBV. The treatment of the underlying infectious trigger alone tends to lead to suboptimal results. Early recognition and prompt treatment have been shown to improve prognosis with severe cases often requiring chemotherapy with or without BMT. Clinicians, therefore, need to be alert and suspect this entity in patients with high fever not responding to broad-spectrum antibiotics, organomegaly and characteristic laboratory and histologic findings.

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