Original Article

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Haemophagocytic lymphohistiocytosis in human immunodeficiency virus: a systematic review of literature

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SUMMARY Diagnosis and management of hemophagocytic lymphohistiocytosis (HLH) in patients with human immunodeficiency virus (HIV) infection are scarcely described in the published literature. The aim of this systematic review was to delineate the triggers of HLH in patients with HIV and understand the role of steroids in the management. We conducted a comprehensive search of English medical literature *via* the Medline / PubMed database using different synonyms of "HIV" AND "HLH". The review was registered in PROSPERO (CRD42018099987). The titles and abstracts of the 185 articles between January 1986 and April 2018 were reviewed. The final analysis was done from 42 articles with 52 patients. HLH was associated with malignancy in 17 patients, while infection was found in 25 patients. No cause was identified in eight patients, out of which four had acute HIV infection. Death was reported in 21 patients. Presence of either malignancy (p = 0.051) or opportunistic infection (p = 0.69) was not associated with increased chances of death by univariate analysis. A total of 26 patients were treated with steroids, while etoposide was used in only four patients. Administration of steroids as a treatment of HLH was associated with more chances of death (p = 0.048). Malignancy and Opportunistic infections are important triggers for HLH in patients with HIV. Acute HIV by itself can act as a trigger for HLH. Evidence on the use of steroids as a treatment of HLH in patients with HIV is not convincing.

Keywords infections, malignancy, steroids

1. Introduction

Hemophagocytic lymphohistiocytosis (HLH) is a hyper-immune condition characterized primarily by fever, bi-cytopenia, hyper-ferritinemia, and hemophagocytosis (*1*). HLH is usually triggered by malignancy, infection, drugs or auto-immune conditions. With the increase in knowledge and understanding of the disease, there is an increase in the number of reported cases of HLH. HLH in human immunodeficiency virus (HIV) infected patients is a rarely described condition in published literature. It is postulated that HLH in HIV patients can be either be due to a co-existent malignancy/ infection or due to uncontrolled replication of HIV itself (*1*). The diagnosis and management of HLH in HIV patients are usually made according to the HLH 2004 criteria and management protocol (*2*). It is tricky to diagnose HLH in HIV infected patients as there is a vast overlap in the clinical and laboratory manifestations of HLH and advanced HIV disease. The treatment of HLH is immunosuppressive therapy (steroids, etoposide and cyclosporine) (*3*). The decision to administer immunosuppressive therapy in an already immunocompromised patient (HIV) is a difficult decision to make. The aim of this systematic review (SR) was to delineate the number of reported cases of HLH, their triggering factors, treatment and outcome in patients with HIV.

2. Methodology

2.1. Search strategy

We first searched for any existing SR on HIV-HLH. Although narrative reviews were present, no SR was identified. We conducted a comprehensive search of English medical literature between January 1986 and April 2018 *via* the Medline/PubMed database. We used ("HIV" OR "human immunodeficiency virus" OR "AIDS" OR "acquired immune deficiency syndrome")

AND ("HLH" OR "haemophagocytic syndrome" OR "hemophagocytic syndrome" OR "haemophagocytic lymphohistiocytosis" OR "hemophogocytic lymphohistiocytosis" OR "hemophagocytosis" OR "haemophagocytosis") as the search terms.

2.2. Inclusion and exclusion criteria

All case studies and case series (prospective or retrospective), where individual patient data were available were included. Those patients where at-least four of the eight HLH criteria were fulfilled were included. Those articles where any of the individual patient data of the following parameters were not present in the paper were excluded: age, sex, details of antiretroviral therapy, CD4 count, the trigger for HLH (malignancy/infection/others), details of anti-HLH treatment (steroids/etoposide) and outcome (discharged/death).

2.3. Study selection

The titles and abstracts of the 185 articles were reviewed independently by two authors (FF and NG) to find cases with both HIV and HLH (Figure 1). In case of any disagreement on study selection between the two authors, the third author (AM) was consulted. Nineteen articles were excluded because they were not in English. A total of 48 articles were excluded because the patient did not have either HIV or HLH or both. Seventeen articles were excluded because they were non-case studies (narrative reviews/perspectives). A total of 101 articles were included for analysis. Full articles were not available for ten articles. Out of the 91 remaining articles, 49 articles were excluded because they did not meet or did not mention the fulfilment of the HLH 2004 diagnostic criteria or did not meet the inclusion criteria. Individual patient data were then extracted from 42 articles (number of patients: 52) (Figure 1) (*4-45*).

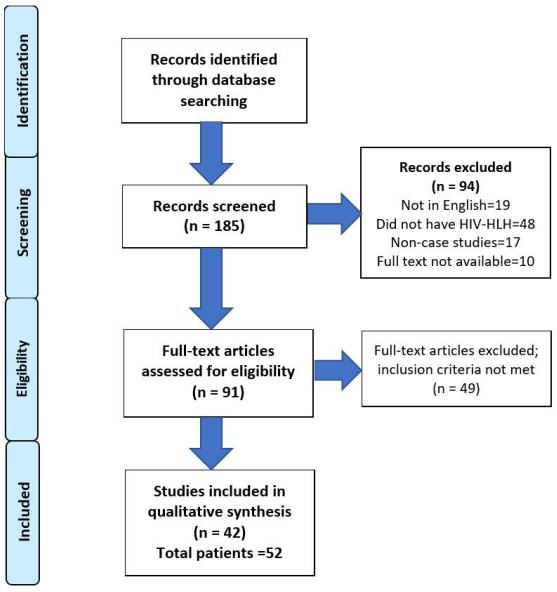

Figure 1. PRISMA flow diagram of the literature search and eligibility for cases with HIV and HLH.

2.4. Data extraction

The following study and patient characteristics were extracted on a pre-designed spreadsheet: age, sex, acute/chronic HIV, treatment-naive/experienced, the regimen of anti-retroviral therapy (ART), the trigger for HLH (malignancy/infection/others), the details of criteria fulfilled, anti-HLH treatment (steroids/etoposide) and the outcome (discharged/death).

2.5. Statistical analysis

Continuous data were presented as mean ± standard deviation (for normally distributed variables) or median and interquartile range when standard deviation was more than 50% of the mean (extremes of data). The frequency of categorical variables was expressed in numbers and percentage. All analyses were done using STATA version 13. PROSPERO registration number: CRD42018099987.

3. Results

A total of 52 cases of HIV and HLH were reviewed. Out of these, 42 (80.8%) were male. The mean age was 38.2 +/– 14.2 years. The median CD4 count at the time of diagnosis of HIV with HLH was 41/µL (IQR: 8-94/µL). Only 17 patients were on antiretroviral therapy (ART) at the time of diagnosis. Of these, a total of seven patients were virologically suppressed at the time of diagnosis of HLH. A total of 26 patients were treated with steroids, while etoposide was used in only four patients (*6-8,8,11-14,16,18,20,23,24,27,30-37,41,44*). Death was reported in 21 patients (*6,12-15,20,27,29,31,36-41,44*). Steroids, when given as a part of HLH management, was associated with increased mortality ($p = 0.048$).

The details of the fulfilment of HLH 2004 criteria is summarized in Table 1 and 2. HLH was associated with malignancy in 17 patients (*6-8,11,12,15,29-31,35-37,39,44*). Infection was associated with HLH in 25 patients (*4,9,10,13,14,17-20,24,26,28,32,33,38,41-43*). In two patients, both malignancy and infection were attributed as the cause for HLH (Table 3) (*34,40*). Some studies reported the frequency of infections or malignancies in patients with HIV and HLH, but they were excluded from the analysis as individual patient data were not available in these studies (*47,48*). When the data from these studies were also combined in the analysis, out of 174 cases with HIV and HLH, 85 had malignancy, 72 had infections, six had both and no cause was identified in 11 patients (*47,48*). Presence of

either malignancy ($p = 0.051$) or opportunistic infection ($p = 0.69$) was not associated with increased chances of death.

No cause was identified in eight patients, out of which four had acute HIV infection (*5,21-23*). All eight patients had a significantly high viral load. Only one patient was on ART at the time of diagnosis (*27*). This patient was diagnosed with HLH as a manifestation of immune reconstitution inflammatory syndrome (IRIS) and died soon after presentation. Rest of the seven patients were started on antiretroviral treatment. Three patients received adjunctive steroids also (*16,23,27*). All seven of these patients improved.

Table 1. Mean/Median of laboratory parameters in patients with HIV & HLH

Parameters	Number[#]	Mean/Median	SD/IQR
Ferritin[*]	43	15,000	4,392-31,435
Haemoglobin	52	8.12	2.68
Total leucocyte count[*]	37	2,540	1150-3750
Platelet count[*]	51	41,000	12,000-80,000
Triglyceride levels[*]	33	312	257-431
Fibrinogen levels[*]	14	168	90-273

[#]Number of patients where the data was available. [*]Median with interquartile range.

Table 2. HLH criteria in patients with HIV & HLH

HLH 2004 diagnostic criteria	Frequency
Hyperferritenemia	42/43
Anaemia	40/52
Fever	52/52
Leucopenia	22/30
Thrombocytopenia	47/51
Hyper TG	24/33
BM showing phagocytosis	39/45
Low NK	2/5
Splenomegaly	42/46
Hypofibrinogenemia	6/15
Increased CD25	10/11

4. Discussion

HLH in HIV, although not common, is well reported and is associated with increased mortality. In a study by Grateau *et al.*, HLH was reported in 0.6% of the patients with HIV (*46*). In a series of patients with infection-associated HLH, concomitant HIV was present in 50% of the patients (*47*). Patients with HIV are predisposed to HLH because of the hyper-inflammatory response due to the increased cytokines (*48*). Increased cytokine levels may be triggered by the opportunistic infection or malignancy or acute HIV itself (*48*). Managing HLH in the setting of HIV infection could be very challenging as treatment focuses on immunosuppression (with steroids, etoposide, *etc.*) which may complicate the course of illness in an already immunocompromised host. The current SR was done to study the profile of patients with the aim of determining the common causes associated with HLH in HIV and their outcome.

Following our search strategy, a total of 52 individual cases were analyzed. HLH was more commonly reported with infections (48%) than malignancy (33%). There was no difference in the mortality between the two groups.

No cause could be identified in 8 cases (19%); however, 4 out of these 8 had acute HIV, and all 8 had a high HIV viral load. Acute HIV is known to be associated with high levels of viraemia. HIV viraemia is associated with changes in cytokine levels (*49*). Presence of viraemia and consequent cytokine changes may have some association with the occurrence of HLH. Unlike HLH due to opportunistic infections or malignancy in HIV, HLH in patients with acute HIV had good prognosis (*21*). Most patients recovered with ART alone (*50*). The fact that viraemia may be associated with HLH and ART may have some role in the treatment of patients with HIV and HLH is suggested by the fact that only 7 out of 52 patients were virologically suppressed. Also, according to the study by Fardet *et*

Table 3. Triggers for HLH in patients with HIV

Trigger	This study	Fardet *et al.*(*48*)	Lerolle *et al.*(*47*)
Number	52	43	19
Malignancy			
Lymphoma	11	16	
Kaposi Sarcoma	6	3	
Multicentric Castleman disease		5	
Infections			
Fungal	Histoplasmosis-15, penicilliosis-1, invasive candidiasis-1, invasive aspergillosis-1	Histoplasmosis-1	
Parasitic	Leishmaniasis-1, Toxoplasmosis-2	Toxoplasmosis-2	Toxoplasmosis-2
Bacterial	Bartonellosis-1	Typhoid-1 *Pseudomonas aeruginosa*-1	*Escherichia coli*-1 *Legionella*-1
Viral	Cytomegalovirus-2, Epstein-Barr virus-1	Cytomegalovirus-2	Cytomegalovirus-1 Herpes Simplex virus 2-1
Tuberculosis	1	8	4
Combined	2		7

al., the mortality of HLH in patients with HIV was considerably higher in the pre-ART era (1981-1996) compared to the ART era (*48*). In our SR, only three patients were from the pre-ART era, one of whom died.

The diagnosis of HLH was made using the HLH 2004 criteria. According to this protocol, to make a diagnosis of HLH, five out of eight criteria should be fulfilled. Since many studies made a diagnosis of HLH prior to the protocol being published, details of individual criteria were often not quoted. Besides, CD25 levels and NK cell activity are resource-intensive, and many studies did not mention it. For this reason, we took those cases that were diagnosed as HLH and had the details of at-least four positive criteria. The most consistent clinical finding was fever (100%), followed by splenomegaly (91%). Amongst the laboratory parameters, hyper-ferritinemia (98%) and thrombocytopenia (92%) were most commonly reported. Bone marrow results were available for 45 cases out of which 39 (86%) patients showed evidence of hemophagocytosis. CD25 values were available only for 11 cases, but 10 (91%) showed increased expression.

The therapy for secondary HLH aims at treating the underlying cause and suppressing the hyper-inflammatory response with immunosuppressants such as corticosteroids (*51*). Mortality was reported in 40% of the patients. Although the consensus statement of experts of histiocyte society recommends steroids for treatment of HLH in patients with HIV, we found that use of steroids in patients with HIV and HLH was associated with higher mortality (*3*). There is a need for large scale prospective studies to understand the role of steroids in the treatment of HLH.

Limitations: Individual patient data were not available in certain large series which were eventually excluded from the analysis. Some series were excluded because they weren't in the English language or their full text could not be accessed. We used four criteria instead of five criteria to make the diagnosis of HLH to increase the sensitivity.

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