Haemophagocytic lymphohistiocytosis in a UK adult population living with HIV

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INTRODUCTION

Haemophagocytic lymphohistiocytosis (HLH) is a syndrome characterised by severe systemic inflammation and abnormal immune activation leading to a cytokine storm which can be fatal. One of the cardinal features of HLH is hyperferritinaemia (ferritin >500 ng/mL). Other features include high fever, cytopenias, hypertriglyceridaemia or hypofibrinogenaemia, splenomegaly and haemophagocytosis seen on bone marrow, lymph node or splenic biopsy. Along with high levels of soluble CD-25 and low NK cell activity, these values are used within the 2004 HLH-protocol criteria to diagnose HLH.

HIV and associated opportunistic infections are a common cause of HLH. Furthermore HLH is an important contributor to mortality in people with advanced HIV. Early treatment of the condition with immunomodulatory medications can halt the progression of HLH, and thus prompt recognition is vital. Untreated HLH carries a very high mortality, especially in patients with advanced HIV.

In this study we looked at eight years of patient data at one HIV centre to investigate the recognition, investigation and treatment of HLH in people living with HIV (PLWH).

AIMS / METHODS

We searched the Royal Free Hospital HIV database for any patient admitted between 2008 and 2016 with a ferritin >2500 ng/mL. This higher value was selected on the basis of HIV itself being a recognised cause of elevated ferritin levels. The patients' electronic results and letters were reviewed to establish whether the five following criteria of HLH-2004 had been measured, and if so, whether the values fulfilled the diagnostic criteria The other two measurements required by the HLH-2004 guidelines (NK-cell activity and soluble CD-25) were excluded as they were rarely assessed at this centre.

Table 1: HLH-2004 Diagnostic Criteria

Marker	Result fulfilling HLH-2004 diagnostic criteria
Temperature	Fever >38 deg C
Full blood count	Cytopaenia in >2 lines
Spleen size	Splenomegaly >14cm
Triglycerides/Fibrinogen	Hypertriglyceridaemia >3 Hypofibrinogenaemia <1.5
Biopsy (bone marrow/lymph node/splenic)	Haemophagocytosis

An established diagnosis of HLH is made when five out of the eight criteria are positive. As only six criteria were measured in this population we defined an established diagnosis when four of the six measured criteria were met.

We also identified which other investigations had been sent during the admission to investigate hyperferritinaemia and possible triggers of HLH. This included viral serology, viral PCR, cultures and serum markers of infection. Outcomes measured assessed included intensive care admission, length of stay, death during admission, diagnosis on discharge or death and treatment given.

RESULTS

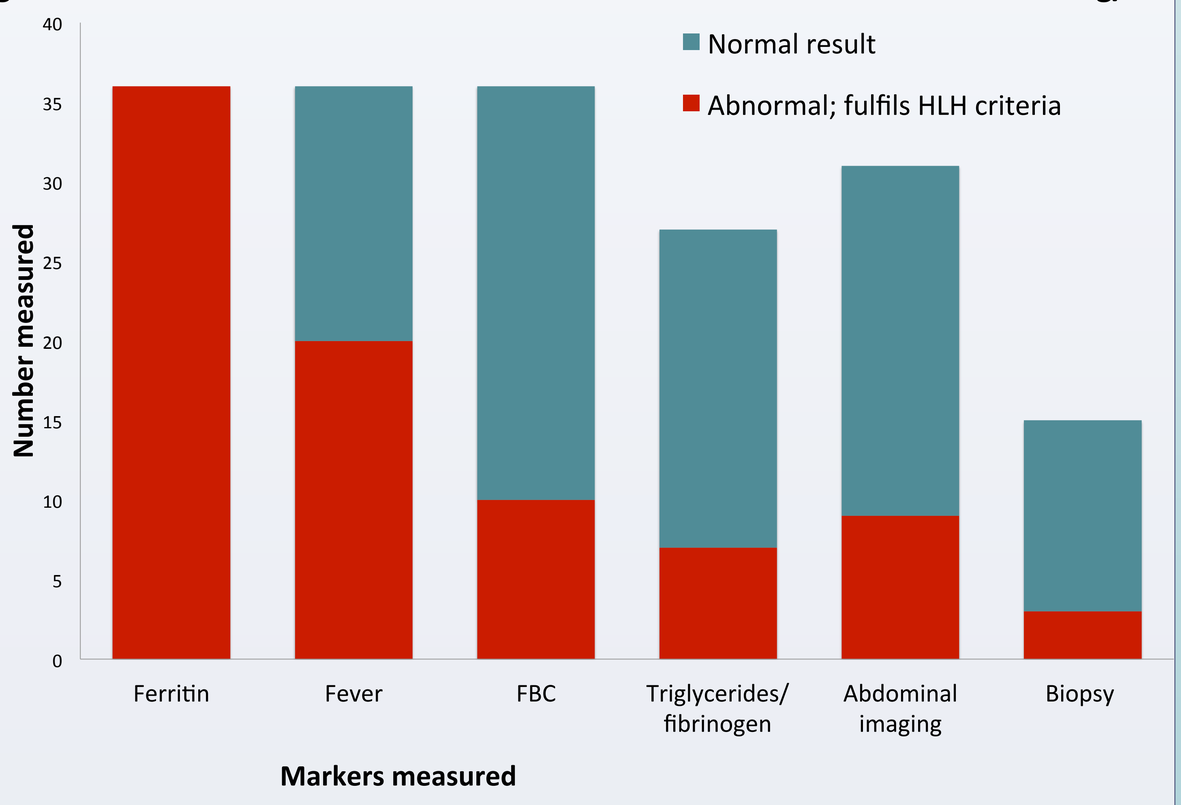
Over 2008-16 there were 36 PLWH who had a measured ferritin >2500 ng/mL (Table 2). Median ferritin 4,812 ng/mL, range 2,514 - 30,355 ng/mL.

Table 2: Demographics of patients

		No (%)
Gender	Male	30 (83%)
	Female	6 (17%)
Age, years	<40	11 (31%)
	> 40	25 (69%)
	Median	48
CD4 count, cells/µL	<200	21 (58%)
	> 200	15 (42%)
	median	121
HIV load, copies/nL	< 50	13 (36%)
	50-500	2 (5%)
	>500	21 (58%)
	median	11,000
ARV treatment	Yes	27 (75%)

Of the 36 patients with ferritin >2500 ng/mL, all had their temperature and full blood count measured, 86% had abdominal imaging, 75% had triglycerides or fibrinogen measured and 43% had a relevant tissue biopsy. Figure 1 shows the proportion of values meeting HLH diagnostic criteria:

Figure 1: Number of HLH-2004 criteria measured in PLWH with ferritin >2500 ng/mL



A variety of different tests were sent for each patient to investigate possible infective triggers of their illness (Table 3).

Table 3: Investigations for infective triggers in PLWH and ferritin >2500 ng/mL

	Viral serology			Viral PCR								Fungal/Parasitology					Cultures	
test	EBV	CMV	HBV/ HCV	CMV	EBV	HHV6	HHV8	PARVO	HSV	VZV	TOXO	CRAG	BDG	GAL	HISTO	LEI	BLD	TB
% tested	28	42	69	75	53	28	25	36	33	25	53	58	8	36	15	15	78	58

Of the 14 PLWH who had all six HLH criteria measured, four (29%) fulfilled 4 or more of the diagnostic criteria, suggesting an established diagnosis of HLH (Table 4). Two had haemophagocytosis on bone marrow (50%).

Table 4: Details of four PLWH with HLH

Final diagnosis	Ferritin	CD4 count	HIV load	ICU admission	Death
Disseminated *M. tuberculosis*, CMV	6500	8	898,726	N	N
Multicentric Castleman, disseminated *M. kansasii*	5234	21	139074	Y	Y
HLH, cardiomyopathy, sepsis	25,248	22	9041380	Y	Y
HLH	30,355	4	3919	Y	Y

Of the other 14 patients, 10 who did not meet HLH diagnostic criteria, had a lower median ferritin level (8,141 ng/mL) and all survived.

CONCLUSION

Despite ferritin being a non-specific marker, when it is significantly elevated in adult PLWH the possibility of HLH should be considered and investigated using a structured set of investigations. In our study only 39% of PLWH with ferritin >2500 ng/mL had all 6 HLH criteria measured.

Measuring the other markers of HLH is important to ensure prompt diagnosis and treatment that may reduce the chance of death. Formulation of a national or local guideline to advise which investigations are required, and when, may be of help to both clinicians and their patients.

This study confirms the high mortality in PLWH with diagnostic criteria for HLH and advanced HIV. Recently, new targeted treatments for HLH have emerged, such as the IL-1 antagonist Anakinra. The increasing availability of more effective treatment options further highlights the importance of early recognition of this condition.