Haemophagocytic lymphohistiocytosis in Hong Kong children have a wider clinical spectrum

To the Editor—We read with interest Chan et al's report on haemophagocytic lymphohistiocytosis (HLH) in Hong Kong children.[1] Of their seven cases, none was classified as primary HLH but limited by unavailability of molecular testing. No malignancy or connective tissue disease was found. Two of seven were confirmed by serology testing to have Epstein-Barr virus (EBV)–associated HLH. The mean time from onset of fever to initiation of treatment was 24 days. The overall survival rate was 43%. We reviewed our experience during the same period (1991-2006).[2-4] Nine patients (male:female, 5:4; mean age, 7 years) were diagnosed according to guidelines.[5] Their clinical features, laboratory findings, viral aetiology, treatment and outcome are summarised in the Table. Two boys from the same family had X-linked lymphoproliferative disorder triggered by primary EBV infection. The signalling lymphocytic activation molecule–associated adaptor protein (*SAP*) gene deletion was confirmed.[3] The older brother died of multi-organ failure and the younger one was successfully transplanted with mismatch-unrelated cord blood. One had macrophage activation syndrome due to adult-onset Still's disease.[4] One had anaplastic large-cell lymphoma. One had malignant histiocytosis and died of cerebral mucomycosis. She had trisomy 3 by cytogenetic analysis of bone marrow. Four had primary EBV infections alone by serology and EBV DNA measurement in plasma and bone marrow.[2,3] With a mean time of 21 days from onset of fever to initiation of etoposide, steroid with or without cyclosporin-based treatment, the overall survival rate was 78% (median follow-up, 6 years). We reckon relying solely on serological diagnosis could be misleading as these patients may have defective antibody production. Genome quantification of EBV is perhaps warranted in HLH.

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Authors' reply

To the Editor—We concur with Ho et al that haemophagocytic lymphohystiocytosis (HLH) in children does have a wider spectrum. It is not a single disease, and can be encountered in association with a variety of underlying conditions leading to the same hyperinflammatory phenotype. As both the series reported by Ho and Chan have small numbers of cases with heterogeneous primary disorders and triggering factors, the clinical data and survival rate do not represent the whole picture in Hong Kong.

Ho suggests that Epstein-Barr virus (EBV) genome quantification should be performed as there may be false-negative serology due to defective antibody production. In a review of 94 cases of EBV-related HLH, diagnosis of EBV infection was based on either a serology test or by EBV genome detection.[1] All cases were EBV VCA-Gig positive and EBV-PCR positive. While EBV DNA quantification may correlate with disease activity, it does not alter the management of HLH.[1,2] The EBV-HLH is not a milder form, and definitely confers a high mortality. Early institution of etoposide containing treatment can improve survival.[3]

We should encourage a prospective multi-centre collaboration with a uniform protocol for

Hong Kong, or participate in the international HLH study of the Histiocyte Society that is dedicated to improving the quality of patient care. The Hong Kong Paediatic Haematology and Oncology Study Group has been actively performing multi-centre studies in the public hospitals, and should be able to take the leading role in such an HLH study.

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TABLE. Clinical and laboratory parameters of Hong Kong children with haemophagocytic lymphohistiocytosis*

	Case								
	1	2	3	4	5	6	7	8	9
Clinical parameters									
Year of diagnosis	1991	1992	1993	1993	1995	2001	2002	2003	2006
Age (yrs)	3.5	13.5	1.5	2	1.5	3	7.8	17.1	14.3
Sex	M	F	F	M	F	M	F	M	M
Fever >1 wk	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Jaundice	No	Yes	Yes	Yes	Yes	No	No	Yes	No
Splenomegaly (cm)	4	8	1	10	+	+	+	+	2
Hepatomegaly (cm)	8	4	1	10	+	4	+	-	4
Lymphadenopathy	Yes	No	Yes	No	No	Yes	Yes	Yes	Yes
Rash	No	No	Yes	Yes	No	No	Yes	Yes	No
CXR	Normal	Normal	ARDS	PE	PE	Consolidation	PE	Normal	PE, consolidation
Laboratory parameters									
Haemoglobin (g/L)	75	66	79	72	83	70	74	74	77
ANC ($x10^9$ /L)	0.05	0.66	0.36	1.1	0.74	0.4	Low	0.4	0.4
Platelets ($x10^9$ /L)	25	17	98	89	15	13	51	78	73
Fibrinogen (g/L)	1.26	0.5	Low	0.91	0.5	N/D	Low	2.36	2.9
Triglyceride (mmol/L)	3.19	5.09	2.98	1.74	7.28	N/D	3.1	4.3	3.06
Ferritin (pmol/L)	N/D	N/D	N/A	1848	N/D	N/D	26 100	>33 000	2545
Bilirubin (μmol/L)	8	280	Elevated	44	83	3	5	41	17
ALT (IU/L)	228	394	Elevated	451	160	152	391	555	11
Haemophagocytosis	BM	BM	BM	BM, liver and lung	Lung	BM	BM	LN	BM
CSF	Pleocytosis	Normal	Pleocytosis	Pleocytosis	Normal	Pleocytosis	Normal	N/D	Normal
NK cells No. (per μL) / cytotoxicity†	256/8.7%	N/D	Very low/im-paired function	N/D	N/D	189/3.8%	N/D	540/5.4%	57/14.1%
EBV DNA	BM and plasma+ve	BM and plasma+ve	BM and plasma+ve	BM, CSF and pleural fluid plasma+ve	N/D	Plasma+ve	Plasma+ve	N/D	N/D
Treatment, causes, and outcome									
Cause	Primary EBV infection	Malignant histiocytosis	Primary EBV infection	XLP/Primary EBV infection	Primary EBV infection	XLP /Primary EBV infection/ primary CMV, HHV6 and HHV7	Primary EBV infection	Still's disease	Anaplastic large-cell lymphoma
Time from onset of fever to initiation of treatment (days)	22	24	28	12	7	17	22	31	27
Treatment	MP + VP16 + acy + IT MTx	MP + VP16 + acy + IT MTx	MP + acy	MP + VP16 + acy	MP + VP16 + CSP + acy	Dexa + VP16 + CSP + anti-CD20 + FOS, followed by MMUC	Dexa + VP16 + CSP + acy	MP + VP16 + CSP	Dexa + VP16 + CSP + acy, followed by lymphoma protocol
Outcome	Full recovery, no recurrence	Died	Full recovery, no recurrence	Died	Full recovery, no recurrence	Full recovery, no recurrence	Full recovery, no recurrence	Full recovery, no recurrence	Full recovery, no recurrence
Special features	-	Trisomy 3 and non-random X inactivation in BM	Fulminant hepatic failure	-	-	-	Pericardial effusion	LN shown eryth-rophagocytosis, extrapulmonary TB, CMV retinitis	Extensive mediastinal and abdominal lymphadenopathy

* acy denotes acyclovir; ALT alanine transferase; ANC absolute neutrophil count; ARDS adult respiratory distress syndrome; BM bone marrow; CMV cytomegalovirus; CSF cerebrospinal fluid; CSP cyclosporine A; CXR chest X-ray; Dexa dexamethasone; EBV DNA Epstein-Barr virus genome; FOS foscarnet; HHV human herpes virus; IT MTx intrathecal methotrexate; LN lymph node; MMUC mismatched unrelated cord blood transplant; MP methylprednisolone; N/A not available; N/D not done; PE pleural effusion; TB tuberculosis; VP-16 etoposide; and XLP X-linked lymphoproliferative disorder

† Absolute number of CD3-CD16/56+natural killer (NK) cells/numerical values of % cytotoxicity for effector cell (mononuclear cell): target cell (51Cr-labelled K562 cells)