marrow (BM), liver, spleen, lymph nodes, skin, and central nervous system (CNS) [3,4]. FHL is a fatal disease if allogeneic hematopoietic stem cell transplantation (SCT) has not been successfully performed.

Epstein–Barr virus (EBV)-associated HLH (EBV-HLH) is a severe form of secondary HLH more frequently occurring in Asian children [5–7]. Activated EBV-infected $CD8^+$ T cells account for the disease process of EBV-HLH [8], however no predisposing factors have yet been clarified. EBV-HLH patients mostly respond to immunochemotherapy, but a small fraction of patients experience a fatal course without SCT. Therefore, although numbers were still small, SCT has been included in the salvage for refractory EBV-HLH cases [9–11]. The optimal timing of SCT, the source of donor cells and the conditioning are critical, particularly for young HLH patients. In this setting, the appropriate SCT for HLH patients needs to be established.

This study analyzed the outcomes of patients with FHL or EBV-HLH who underwent SCT in Japan over the past 10 years, in order to address the issues in the transplant-related problems including engraftment, late sequelae as well as to find out if there are distinct transplant strategies for FHL and EBV-HLH patients.

PATIENTS AND METHODS

Data Collection

The HLH/LCH Committee in the Japanese Society of Pediatric Hematology (JSPH) sent the first questionnaires to the hospitals administered by JSPH members based on the SCT registry in JSPH, asking if SCT was performed for any HLH patients between 1995 and 2005. The second questionnaires were sent to 57 hospitals with SCT cases, asking the patients' characteristics, treatment prior to SCT, donor sources, conditioning regimens, complications, and outcome. Of the 47 responses (recover rate 82%), 61 definite SCT cases from 33 hospitals were eligible for the study (mean 1.7 case/hospital, Supplemental Table). Forty-three FHL patients underwent 46 SCT, while 14 EBV-HLH patients underwent a total of 15 SCT. The majority of SCT (EBV-HLH 87%, FHL 89%) were performed between 2000 and 2005.

Diagnosis and Classification

All 57 patients fulfilled the diagnostic criteria of HLH [12]. FHL was diagnosed when the patient had a genetic abnormality, positive family history, and/or other evidence such as impaired natural killer cell activity [13]. The genetic study of FHL 2, 3, and 4, approved by the ethics committee of Kyushu University, Japan (No. 45), was partly completed postmortem according to our methods [14–17]. FHL2 and FHL3 determined by *PRF1* or *UNC13D* mutations accounted for 28% (n = 12), and 26% (n = 11), respectively, in this group. In addition, a total of eight patients were found with siblings diagnosed as having HLH. EBV infection might be associated with the development of HLH in four FHL patients (one FHL2, one FHL3, and two familial). These cases were classified as FHL, not as EBV-HLH. Other types of primary HLH such as XLP were excluded in this study.

EBV-HLH was diagnosed when a non-FHL patient had a primary infection or reactivation of EBV at the onset of HLH. EBV infection was assessed by the detection of EBV DNA and/or the pattern of serum EBV-specific antibody titers [18]. Cases with secondary HLH occurring in a chronic active EBV infection [19], and/or a histologically confirmed EBV-related lymphoma were excluded in this study. CNS involvement was determined when patients showed neurological manifestations, clinically as well as with any evidence of abnormality in the cerebrospinal fluids (CSF), neuroimagings (CT/MRI), and/or electroencephalography (EEG).

Prior Treatment to SCT

Treatment was based on the HLH-94 protocol using a combination of corticosteroid, cyclosporine-A (CSA), and etoposide (VP16) for both groups [20,21]. As the multidrug chemotherapy, CHOP-VP16-based regimen (VP16, vincristine, cyclophosphamide [CY], doxorubicin, and prednisolone) was chiefly employed. SCT was performed for all FHL patients, but limited for EBV-HLH patients who were resistant to any other treatments.

SCT

Allogeneic SCT was performed in 53 of the 57 patients (93%). Autologous SCT and identical-twin donor SCT were performed in three and one sporadic patients, respectively, because the molecular diagnosis was not available at the time of SCT. Donor sources, infused cell doses, conditioning regimens, and other SCT-related data are summarized in Table I. Allogeneic donor sources for EBV-HLH were HLA-matched sibling peripheral blood (PB) 1, haploidentical parent BM/PB 2, HLA-matched unrelated BM 1, HLA-matched unrelated cord blood (UCB) 2, and HLA-mismatched UCB 5, and those for FHL were HLA-matched related BM 7 (sibling 6), haploidentical parent BM/PB 2, HLA-matched unrelated BM 12, HLA-matched UCB 9, and HLA-mismatched UCB 12. All CBs were obtained from unrelated donors registered in the Japanese Cord Blood Bank Network. All unrelated donor BMs were obtained from the Japanese Marrow Donor Program. Myeloablative conditioning for EBV-HLH included VP16/busulfan (BU)/CY in 8 patients (4 in UCB transplantation [UCBT]) and other regimens in 3 patients, while those for FHL were VP16/BU/CY plus or minus anti-thymocyte globulin (ATG) in 23 patients (10 in UCBT) and others in 8 patients. Reduced intensity conditioning (RIC) for EBV-HLH included melphalan (MEL)/fludarabine (FLU) plus or minus thoracoabdominal irradiation in three patients (two in UCBT), and those for FHL were MEL/FLU plus or minus low-dose total body irradiation plus or minus ATG in eight patients (four in UCBT) and others in three patients. Donor chimerism was assessed by using short tandem repeats or sex chromosome analyses.

Evaluation of Late Sequelae

Long-term survivors were further questioned concerning their physical growth, endocrinological status, and neurological deficits. Neurological development including cognitive functions was assessed by Karnofsky score, developmental quotient and/or school performance.

Statistical Analysis

The 10-year overall survival (OS) rate with 95% confidence intervals were estimated by the Kaplan–Meier method. The OS was calculated for the period from the day of SCT until the death of any cause or the final observation. All results were updated to May 31,

TABLE I. Profiles of Patients Who Underwent Hematopoietic Stem Cell Transplantation

	EBV-HLH	FHL	*P*-value
Number, male:female	14, 4:10	43, 23:20	0.37
Age at onset (median, range)	5.5y, 6m–18y	0.5y, 6d–12y	<0.0001
Age at SCT (median, range)	5.9y, 1.4–18y	1.2y, 0.4–15y	0.0002
Observation period (median, range)	5.5y, 0.3–16y	4.8y, 0.2–19y	0.94
Manifestation at diagnosis (%)			
Fever	100	95	>0.99
Hepatosplenomegaly	86	86	>0.99
Lymphadenopathy	36	21	0.30
Skin eruption	7	14	0.67
Respiratory failure	36	14	0.12
DIC	50	33	0.26
Treatment prior to SCT (%)			
HLH94 only	36 (5/14)	60 (25/42)	0.14
Multidrug chemotherapy	57 (8/14)	19 (8/42)	0.017
Diagnosis to SCT (median, range)	5.8m, 1.8–24m	7.5m, 1.6–84m	0.18
SCT (n)			
Allogeneic	11	42	
Auto/Identical twin	3	1	
Nucleated cell doses ($\times 10^8$/kg)	1.3 (0.2–6.6)	2.5 (0.1–12.7)	0.14
Donor			
UCB	7	21	0.94
Others	7	22	
HLA disparity no	4	28	0.09
HLA disparity yes (>1 locus[a])	7	14	
Conditioning			
Myeloablative[b]	11	31	>0.99
RIC[c]	3	11	
Irradiation yes	4	11	0.73
Irradiation no	9	31	
ATG yes	0	8	0.18
ATG no	14	34	
CNS abnormality (%)			
At diagnosis	29[d] (4/14)	21[d] (9/42)	0.72
Before SCT	57 (8/14)	67 (28/42)	0.52
CSF pleocytosis	25 (2/8)	32 (7/22)	>0.99
MRI abnormality	36 (5/14)	51 (20/39)	0.36
Convulsion	43 (6/14)	41 (17/41)	0.93
Disturbed consciousness	36 (5/14)	24 (10/41)	0.49
Post-transplant state (n)			
Early death (<100 days)	2	7	0.48
Alive	12	29	0.31
Neurological deficit (%)	8[d] (1/12)	29[d] (7/24)	0.22
Late sequelae[e] (%)	8 (1/12)	52 (11/21)	0.022

ATG, anti-thymocyte globulin; BU, busulfan; CNS, central nervous system; CSF, cerebrospinal fluid; CY, cyclophosphamide; DIC, disseminated intravascular coagulopathy; EBV, Epstein–Barr virus; FHL, familial hemophagocytic lymphohistiocytosis; FLU, fludarabine; HLH, hemophagocytic lymphohistiocytosis; MEL, melphalan; MRI, magnetic resonance imaging; SCT, hematopoietic stem cell transplantation; TAI, thoracoabdominal irradiation; TBI, total body irradiation; UCBT, unrelated donor cord blood transplantation; VP16, etoposide. Parenthesis means the positive number of patients per the evaluable number of patients. The observation period means the time from the onset to the last visit or death. [a]Human leukocyte antigen (HLA) disparity was assessed by the serotyping data of HLA-A, -B, and -DR; [b]Myeloablative conditionings for EBV-HLH were VP16/BU/CY 8 (4 in UCBT) and others 3, and those for FHL were VP16/BU/CY + ATG 23 (10 in UCBT) and others 8; [c]Reduced intensity conditionings (RIC) for EBV-HLH were MEL/FLU + TAI 3 (2 in UCBT), and those for FHL were MEL/FLU + low dose TBI + ATG 8 (4 in UCBT) and others 3; [d]The proportion of patients having neurological abnormality was lower in survived patients with EBV-HLH ($P = 0.0015$). Survived patients were neurodevelopmentally assessed at the last visit to the hospital; [e]Late sequela(e) in EBV-HLH was hemiparesis (n = 1), and those in FHL were short stature (n = 5), endocrinological abnormality (n = 1), psychomotor retardation with or without seizure (n = 5), brain atrophy (n = 1), and hearing difficulty (n = 1).

2008. An analysis of the risk factors for SCT outcome was possible for FHL, but not for EBV-HLH because of the small number of subjects. Age at onset of HLH or at the SCT, duration from the onset to SCT, CNS disease before SCT, donor sources, and the type of conditioning were tested using the log-rank method. Cox proportional-hazard model was employed to examine the association between selected clinical variables and the risk for death. A logistic regression model was used to investigate factors associated with neurological sequelae. Chi-square test or Fisher's exact test were employed in other comparisons. P values less than 0.05 were considered to be significant.

RESULTS

Profiles of EBV-HLH and FHL Patients

A comparison of the clinical profiles (Table I) revealed that the ages at disease onset and at the time of SCT were each higher in EBV-HLH than in FHL patients ($P < 0.0001$, $P = 0.0002$, respectively). No clinical manifestations differed between the two groups during the disease course, including respiratory failure as well as CNS abnormalities at diagnosis. The proportion of patients who failed VP16 and CSA therapy including HLH94 protocol and needed combination chemotherapy such as CHOP-VP16 before planning SCT was higher in EBV-HLH patients than FHL patients (57% vs. 19%, $P = 0.0168$).

Outcomes of SCT

Engraftment and survival. Post-transplant outcomes of 43 FHL patients and 14 EBV-HLH patients are summarized in Figures 1 and 2. The 10-year OS rates (median ± SE%) of FHL and EBV-HLH patients were 65.0 ± 7.9% and 85.7 ± 9.4%, respectively ($P = 0.24$; Fig. 3). In the allogeneic SCT cases with FHL (Fig. 1), 29 attained engraftment, 6 had rejection or graft failure, and 7 were undetermined. On the other hand, in EBV-HLH (Fig. 2), seven were engrafted, three were rejected, and one was undetermined. Of all 29 FHL patients engrafted after the first SCT, 26 were alive with no HLH relapse, but 3 died of treatment-related mortality (TRM). Seven engrafted patients with EBV-HLH were alive and well at the final follow-up. Among the nine rejection/graft failure patients (six FHL, three EBV-HLH), a second UCBT was successful in three of the four patients (three FHL, one EBV-HLH). Twelve of the UCBT recipients for FHL that received a graft with the first UCBT and two that received a second UCBT were alive at the last follow-up; while seven died; six were due to TRM and one was due to active HLH disease. Six of the seven UCBT recipients for EBV-HLH were alive and well at the last follow-up, while only one died of active HLH disease on day 18 post-transplant. A total of 29 FHL survivors after allogeneic SCT(s) had 17 complete donor chimera (2 patients after second UCBTs), 3 mixed chimera (1 had 42% donor chimera in remission 18 months after SCT, 2 attained >90% donor chimera until 6 months after SCT), 8 undefined, and 1 graft failure with CNS disease. Ten EBV-HLH survivors after allogeneic SCT attained eight complete donor chimera (seven patients after the first SCT and one patient after second SCT [UCBT]), and two with autologous recovery. Two of three EBV-HLH patients who rejected allogeneic cells were alive and disease free more than 6 years post-transplant. One of two EBV-HLH patients who underwent autologous SCT was alive and well 13 years post-transplant [22]. One EBV-HLH patient was alive and well 10 years after the identical twin donor BMT.

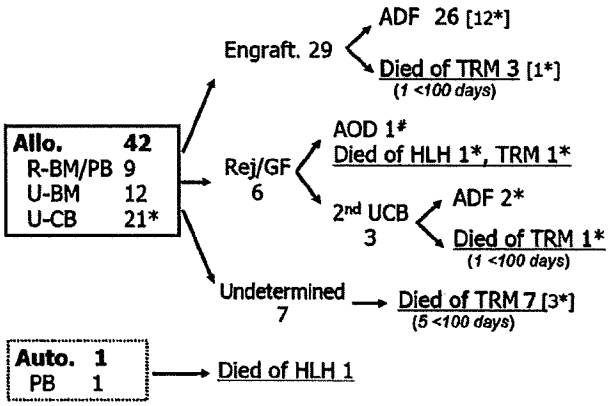

Fig. 1. Cohort diagram for the clinical outcome of 43 patients with familial hemophagocytic lymphohistiocytosis (FHL) who underwent stem cell transplantation (SCT). Of 42 patients after allogeneic SCT, 29 achieved engraftment (18 complete, 3 mixed) and 6 failed to engraft. One (#) with graft failure was alive with central nervous system disease 12 years after SCT. A total of 29 patients (67%) were alive after SCT. The underlined data indicate the number of deceased patients. Seven patients died within 100 days post-SCT (parenthesis). Asterisk (*) means UCB. R, related; U, unrelated; BM, bone marrow; PB, peripheral blood; CB, cord blood; ADF, alive with the disease free state; AOD, alive on disease; Rej/GF, rejection or graft failure; TRM, treatment-related mortality.

Causes of death. Of 14 deceased FHL patients, 12 died of TRM, including 3 chronic GVHD while 2 died of recurrent HLH. Seven patients experienced early death from TRM within 100 days after SCT (Fig. 1). One patient, later diagnosed with FHL2, died of CNS disease 5 years after autologous SCT [14]. Two EBV-HLH patients died of recurrent HLH within 50 days after SCT (Fig. 1). No TRM-related deaths were noted among the EBV-HLH patients.

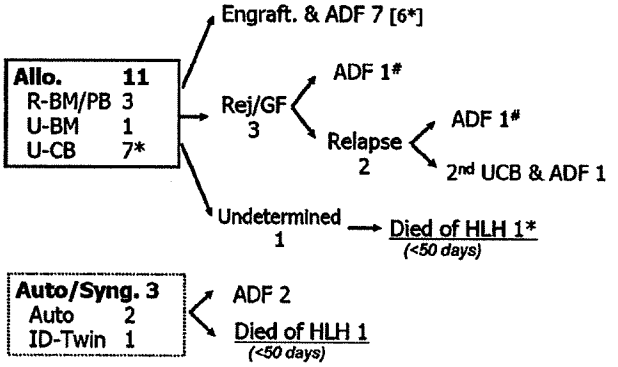

Fig. 2. Cohort diagram for the clinical outcome of 14 patients with Epstein–Barr virus-associated hemophagocytic lymphohistiocytosis (EBV-HLH) who underwent SCT. Among 11 patients after the first allogeneic SCT, 7 achieved successful engraftment and 3 failed to engraft. A total of 12 patients (86%) were alive after SCT. Two patients (#) were alive and well more than 6 years after SCT failure. The underlined data indicate the number of deceased patients. Two patients died within 50 days post-SCT (parenthesis). Asterisk (*) means UCB. Auto/Syng: autologous/syngeneic, ID: identical.

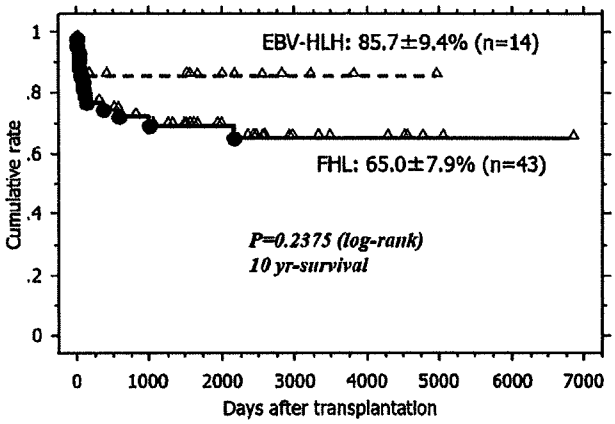

Fig. 3. Cumulative probability of post-transplant overall survival of FHL (*solid line*) and EBV-HLH patients (*dashed line*) who underwent SCT. Closed circle and open triangle represent deceased and alive patients, respectively. Each value indicates the 10-year overall survival rate plus or minus standard error assessed by the log-rank test.

Analysis of Prognostic Factors in FHL

A log-rank test on the OS rate did not show any significant difference in terms of age at SCT (<2 years vs. ≥2 years), time of SCT from HLH treatment (<6 months vs. ≥6 months), conditioning regimens (myeloablative vs. RIC) and various donor sources (R-PB/BM vs. UCBT vs. UBM; Table II). The Cox hazard model with adjustment for gender and age at engraftment indicated that the risk of death for UBM might be higher than that for R-PB/BM (adjusted hazard ratio = 0.07, 95% confidence interval [CI] = 0.01–1.02, $P = 0.05$) and that for UCB (0.27, 95% CI = 0.07–1.09, $P = 0.07$; Table II). No significant variables were found to predict the risk of early death within 100 days post-transplant, or the risk of neurological sequelae.

CNS Abnormalities and Late Sequelae

Table I shows that the frequency of CNS abnormalities at onset and the time of SCT did not differ between the EBV-HLH and FHL patients. Whereas, post-transplant CNS abnormalities were significantly higher in the FHL patients ($P = 0.0015$). Eleven FHL patients (52%) have had late sequelae including neurological as well as endocrinological problems, in comparison to only one EBV-HLH patient with left hemiparesis ($P = 0.022$). Late sequelae of FHL

TABLE II. Association Variables Influencing on the Risk of Mortality in FHL Patients

(A) Log-rank analysis Variables	No.	Survival (OS %)		*P*-value
Age				
<2 years	30	66.2 ± 8.7		0.56
≥2 years	12	75.0 ± 12.5		
Time from HLH treatment				
<6 months	14	62.9 ± 13.3		0.65
≥6 months	28	71.4 ± 8.5		
Conditioning				
Myeloablative	31	71.0 ± 8.2		0.50
RIC	11	60.6 ± 15.7		
Donor sources				
R-PB/BM, a	9	88.9 ± 10.5	a vs. b	0.22
UCB, b	21	65.6 ± 10.6	a vs c	0.15
UBM, c	12	58.3 ± 14.2	b vs c	0.61

(B) Cox's model analysis Variables	No.	Adjusted hazard ratio	95% CI lower–upper limit	*P*-value
Stem cell source				
Unrelated BM	12	1.00	Reference	
Unrelated CB	21	0.27	0.07–1.09	0.07
Related PB/BM	9	0.07	0.01–1.02	0.05
Conditioning				
Reduced intensity	11	1.00	Reference	
Myeloablative	31	0.48	0.09–2.47	0.38
Radiation				
No	31	1.00	Reference	
Yes	11	0.52	0.11–2.52	0.41
Use of ATG				
No	34	1.00	Reference	
Yes	8	0.91	0.18–4.70	0.91
HLA disparity				
No	28	1.00	Reference	
Yes (>1 locus)	14	2.79	0.75–10.38	0.13

Both analyses (A, B) were performed for 42 FHL patients who underwent the first allogeneic SCT. The Cox model analysis was performed with adjustment for selected variables including sex and age at engraftment.

included psychomotor retardation with or without seizures (n = 5), brain atrophy (n = 1), hearing difficulty (n = 1), short stature (n = 5), and impaired sexual development (n = 1).

DISCUSSION

No underlying immunodeficiency has yet been identified for idiopathic EBV-HLH, which has been recognized to be distinct from familial or inherited disease-related HLH like FHL. However, EBV also acts as a trigger in the development of HLH episodes in FHL patients. Therefore, caution must be exercised in the differentiation of the two types of HLH disease. Strict use of the renewed diagnostic criteria for the registered cases in Japan enabled an analysis of the SCT results of 43 FHL and 14 EBV-HLH patients. The data first revealed a high survival rate in UCBT recipients in either type of HLH, indicating that CB could be preferable BM as the unrelated donor source in SCT for pediatric patients with refractory HLH. In addition, SCT in FHL patients was more problematic than that in EBV-HLH, where it was associated with a high incidence of post-transplant early death rate as well as late sequelae including neurological deficits. The EBV-HLH patients showed no apparent sequelae even if they had CNS involvement at diagnosis.

Information concerning SCT for HLH patients has been accumulated mostly in FHL, but little has been published in EBV-HLH except for sporadic case reports [10,11]. Previously published major studies on SCT in FHL patients are summarized in Table III. Because of the historical changes in the available genetic analyses, supportive care practices, donor sources and conditioning, the pre-2000 studies [23–27] might not be comparable to the current data. Henter et al. [21] showed the improved survival of patients treated with HLH-94 followed by BMT, in which the 3-year post-BMT survival was 62%. Horne et al. [28] noted significant TRM due to venoocclusive disease (VOD) after myeloablative conditioning, and that an active disease status at SCT was associated with a poor prognosis. Ouachee-Chardin et al. [29] reported 59% of OS in a series of 48 patients including 60% of haploidentical SCT, and indicated a high TRM due to VOD associated with young age. Recently, Baker et al. [30] reported that BU/CY/VP16 plus or minus ATG-conditioning provided a cure in 53% of patients after unrelated donor BMT, but a high mortality rate at day 100 (32 of 50 [64%] deceased patients). The present study showed a comparably high OS rate (69%) and similarly high incidence of early death until day 100 (7 of 13 [54%] deaths after allogeneic SCT) in Japan. Probably, the major distinction of the current study from the other reports is a higher usage of UCBT (50%) and RIC (26%). Unfortunately, the combined usage of RIC-UCBT was applied only in eight cases (14%) in this study, which was insufficient to fully evaluate its effectiveness. With regard to RIC-SCT with or without UCBT for FHL, Cooper et al. [31] reported a high disease free survival (75%) in 12 HLH patients (including 5 FHL) who underwent RIC-SCT from matched family/unrelated or haploidentical donor, in which 3 of 9 survivors had mixed chimerism but remain free of disease. The most recent report by Cesaro et al. [32] analyzed 61 cases including an appreciable number of RIC (18%) and UCBT (10%), but did not document the superiority of RIC-UCBT. In the present study, UCBT had a tendency to yield a more favorable outcome than UBMT, although the difference was not statistically significant. FHL infants received SCT early; however the fact that survival of FHL patients who underwent SCT at <2 years of age was not better than later SCT might reflect the difficulty in determining the optimal timing of SCT

TABLE III. Reports on the Clinical Outcome of Patients With HLH Who Underwent Allogeneic Hematopoietic Stem Cell Transplantation

No. pts	Median age at SCT (months)	FH (%)	Major conditioning regimen	Donor	Source	OS (%)	Engraft. (%)	Causes of death	Refs.
9	13	45	Myeloab	VP16/BU/CY ±anti-LFA1	MRD/MMRD/haplo	BM	44.0	100	TR, HLH	[24]
29	NR	48	Myeloab	NR	MRD/MUD/haplo	BM	66.0	72	TR, HLH	[25]
20	9	30	Myeloab	VP16/BU/CY ±ATG	MSD/URD (80%)	BM	45.0	90	TR, HLH	[26]
14	14	36	Myeloab	VP16/BU/CY, ATG/BU/CY	MMRD/MUD	BM (T cell depleted)	64.3	65	TR, HLH	[27]
12	18	42	Myeloab	VP16/BU/CY	MSD/URD (67%)	BM	100	100	No	[33]
17	NR	NR	Myeloab	VP16/BU/CY ±ATG, TBI	MRD/URD/haplo	BM, CB (2), PB, CD34	58.0	94	TR, HLH, lymphoma	[8]
65[a]	13	31	Myeloab	VP16/BU/CY ±ATG	MRD/URD/haplo	BM, CB (5), PB, CD34	62.0	89	TR, HLH, AML	[21]
86[a]	13	34	Myeloab	VP16/BU/CY ±ATG, TBI	MRD/URD/haplo	BM, CB (7)	64.0	90	TR, HLH, 2nd AML	[28]
48	6	35	Myeloab	VP16/BU/CY, ATG/BU/CY	MSD/URD/haplo	BM, PB	58.5	78	HLH	[29]
12	14	17	RIC	FLU/MEL ± BUS, FLU/2GyTBI	MRD/URD/haplo	BM, CD34	75.0	100	TR	[31]
91	12	NR	Myeloab	VP16/BU/CY ±ATG	URD	BM, PB, CB (9)	45.0	83	TR, HLH	[30]
61	13	20	RIC (18%)	VP16 or MEL/BU/CY ±ATG	MRD/MMRD/URD	BM, PB, CB (6)	63.9	78	TR (68%), HLH (27%)	[32]
42	17	55	RIC (26%)	VP16/BU/CY ±ATG, TBI	MRD/MMRD/URD	BM, PB, CB (21)	69.0	78	TR (79%), HLH (21%)	Ours

AML, acute myelogeneous leukemia; BM, bone marrow; BU, busulfan; CB, cord blood; CY, cyclophosphamide; FHL, familial hemophagocytic lymphohistiocytosis; FH, family history; FLU, fludarabine; MEL, melphalan; MMRD, HLA-mismatched related donor; MRD, HLA-matched related donor; MSD, HLA-matched sibling donor; MUD, HLA-matched unrelated donor; NR, not recorded; PB, peripheral blood; RIC, reduced intensity conditioning; TBI, total body irradiation; TR, transplantation-related events; URD, unrelated donor; VP16, etoposide. [a]Sixty four of 65 patients studied by Henter et al. [21] were included in 86 patients by Horne et al. [28].

or introducing appropriate RIC regimens in young infants. In UCBT, a major obstacle was thought to be early graft failure, but once engrafted no late graft failure could not be seen [29]. We confirmed this finding in our UCBT cases.

Dürken et al. [33] reported that six HLH patients with CNS disease underwent allogeneic BMT and three of them had no persistent neurological problems after transplant. More recently, SCT is thought to be preferable for FHL patients at the early stage of CNS disease with variable presentation [34,35]. Fludarabine-based RIC has been preferred in SCT for FHL patients in order to reduce late sequelae [36,37]. Since CNS disease itself had no impact on the OS in the current study, but nearly half of the long-term survivors of FHL had late sequelae associated with growth and development, further prospective studies should be focused on how to reduce late sequelae in SCT for FHL patients.

In the treatment of refractory EBV-HLH, no consensus has yet been reached concerning the treatment of patients who fail to respond to the HLH-2004 protocol type immunochemotherapy. Several reports documented that SCT led to a complete remission in such cases [8,10,11,28,38,39]. The present study revealed that use of pre-SCT combination chemotherapy might be associated with a better therapeutic impact on subsequent SCT in patients with EBV-HLH. Furthermore, long-term survival, that is, a probable cure, could be obtained even after autologous SCT [22] or identical twin donor BMT, suggesting that a reconstitution of allogeneic hematopoietic stem cells was not essential in the successful SCT for EBV-HLH patients as described in the autologous PBSCT success for lymphoma-associated HLH [40]. In addition, long-term survival even after graft failure or post-transplant relapse in EBV-HLH patients might suggest the possibility of resetting the adaptive immune response to the virus as postulated in autologous SCT for the treatment of autoimmune diseases [41,42]. Moreover, successful syngeneic SCT may imply that EBV-HLH is not a monogenic disease, since Chen et al. [43] observed that a primary infection of EBV incited HLH in a pair of the twins, but not in the identical twin counterpart. These observations implied that the genetic influence in patients with EBV-HLH might be distinct from that in patients with FHL on precipitating the excessive immune activation. Further prospective studies should therefore be directed toward not only the optimization of UCBT-RIC to improve survival of FHL patients, but to better understanding of the pathological interaction between cytotoxic granule disorders and EBV.

ACKNOWLEDGMENT

We thank all contributors of the Japanese Society of Pediatric Hematology who participate in the treatment of HLH patients (Supplemental Table). This work was supported in part by a Grant-in-Aid for Scientific Research (C) #19591255 (O.S.) from the Ministry of Education, Culture, Sports, Science and Technology of Japan, and a fund of the HLH/LCH Committee in the Japanese Society of Pediatric Hematology. We thank Dr. Brian Thomas Quinn (Associate Professor, Department of Linguistic Environment, Faculty of Languages and Cultures, Kyushu University) for kindly correcting the manuscript.

REFERENCES

1. Janka GE. Familial and acquired hemophagocytic lymphohistiocytosis. Eur J Pediatr 2007;166:95–109.
2. Ishii E, Ohga S, Imashuku S, et al. Nationwide survey of hemophagocytic lymphohistiocytosis in Japan. Int J Hematol 2007;86:58–65.
3. Jordan MB, Hildeman D, Kappler J, et al. An animal model of hemophagocytic lymphohistiocytosis (HLH): $CD8^+$ T cells and interferon gamma are essential for the disorder. Blood 2004;104:735–743.
4. Billiau AD, Roskams T, Van Damme-Lombaerts R, et al. Macrophage activation syndrome: Characteristic findings on liver biopsy illustrating the key role of activated, IFN-gamma-producing lymphocytes and IL-6- and TNF-alpha-producing macrophages. Blood 2005;105:1648–1651.
5. Ohga S, Nomura A, Takada H, et al. Immunological aspects of Epstein-Barr virus infection. Crit Rev Oncol Hematol 2002;44:203–215.
6. Imashuku S. Systemic type Epstein-Barr virus-related lymphoproliferative diseases in children and young adults: Challenges for pediatric hemato-oncologists and infectious disease specialists. Pediatr Hematol Oncol 2007;24:563–568.
7. Cho EY, Kim KH, Kim WS, et al. The spectrum of Epstein-Barr virus-associated lymphoproliferative disease in Korea: Incidence of disease entities by age groups. J Korean Med Sci 2008;23:185–192.
8. Kasahara Y, Yachie A, Takei K, et al. Differential cellular targets of Epstein-Barr virus (EBV) infection between acute EBV-associated hemophagocytic lymphohistiocytosis and chronic active EBV infection. Blood 2001;98:1882–1888.
9. Imashuku S, Hibi S, Todo S, et al. Allogeneic hematopoietic stem cell transplantation for patients with hemophagocytic syndrome (HPS) in Japan. Bone Marrow Transplant 1999;23:569–572.
10. Minegishi M, Ohashi Y, Kumaki S, et al. Successful umbilical cord blood transplantation from an unrelated donor for a patient with Epstein-Barr virus-associated hemophagocytic lymphohistiocytosis. Bone Marrow Transplantat 2001;27:883–886.
11. Toubo T, Suga N, Ohga S, et al. Successful unrelated cord blood transplantation for Epstein-Barr virus-associated lymphoproliferative disease with hemophagocytic syndrome. Int J Hematol 2004;80:458–462.
12. Henter JI, Horne A, Aricó M, et al. HLH-2004: Diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis. Pediatr Blood Cancer 2007;48:124–131.
13. Ishii E, Ueda I, Shirakawa R, et al. Genetic subtypes of familial hemophagocytic lymphohistiocytosis: Correlations with clinical features and cytotoxic T lymphocyte/natural killer cell functions. Blood 2005;105:3442–3448.
14. Suga N, Takada H, Nomura A, et al. Perforin defects of primary hemophagocytic lymphohistiocytosis in Japan. Br J Haematol 2002;116:346–349.
15. Yamamoto K, Ishii E, Sako M, et al. Identification of novel MUN13-14-mutations in familial haemophagocytic lymphohistiocytosis and functional analysis of MUNC13-4-deficient cytotoxic T lymphocytes. J Med Genet 2004;41:763–767.
16. Yamamoto K, Ishii E, Horiuchi H, et al. Mutations of syntaxin 11 and SNAP23 genes as causes of familial hemophagocytic lymphohistiocytosis were not found in Japanese people. J Hum Genet 2005;50:600–603.
17. Ueda I, Ishii E, Morimoto A, et al. Phenotypic heterogeneity of familial hemophagocytic lymphohistiocytosis (FHL) in relation to gene mutational characteristics. Pediatr Blood Cancer 2006;46:482–488.
18. Ohga S, Nomura A, Takada H, et al. Epstein-Barr virus (EBV) load and cytokine gene expression in activated T cells of chronic active EBV infection. J Infect Dis 2001;183:1–7.

19. Okano M, Kawa K, Kimura H, et al. Proposed guidelines for diagnosing chronic active Epstein-Barr virus infection. Am J Hematol 2005;80:64–69.
20. Henter JI, Aricò M, Egeler RM, et al. HLH-94: A treatment protocol for hemophagocytic lymphohistiocytosis. HLH study Group of the Histiocyte Society. Med Pediatr Oncol 1997;28:342–347.
21. Henter JI, Samuelsson-Horne A, Aricò M, et al. Treatment of hemophagocytic lymphohistiocytosis with HLH-94 immunochemotherapy and bone marrow transplantation. Blood 2002;100: 2367–2373.
22. Ohga S, Nomura A, Kai T, et al. Prolonged resolution of hemophagocytic lymphohistiocytosis after high dose chemotherapy followed by autologous peripheral blood stem cell transplantation. Bone Marrow Transplant 1997;19:633–635.
23. Fischer A, Cerf-Bensussan N, Blanche S, et al. Allogeneic bone marrow transplantation for erythrophagocytic lymphohistiocytosis. J Pediatr 1986;108:267–270.
24. Blanche S, Caniglia M, Girault D, et al. Treatment of hemophagocytic lymphohistiocytosis with chemotherapy and bone marrow transplantation: A single-center study of 22 cases. Blood 1991;78: 51–54.
25. Arico M, Janka G, Fischer A, et al. Hemophagocytic lymphohistiocytosis. Report of 122 children from the International Registry. Leukemia 1996;10:197–203.
26. Baker KS, DeLaat CA, Steinbuch M, et al. Successful correction of hemophagocytic lymphohistiocytosis with related or unrelated bone marrow transplantation. Blood 1997;89:3857–3863.
27. Jabado N, de Graeff-Meeder ER, Cavazzana-Calvo M, et al. Treatment of familial hemophagocytic lymphohistiocytosis with bone marrow transplantation from HLA genetically nonidentical donors. Blood 1997;90:4743–4748.
28. Horne A, Janka G, Maarten Egeler R, et al. Haematopoietic stem cell transplantation in haemophagocytic lymphohistiocytosis. Br J Haematol 2005;129:622–630.
29. Ouachee-Chardin M, Elie C, de Saint Basile G, et al. Hematopoietic stem cell transplantation in hemophagocytic lymphohistiocytosis: A single-center report of 48 patients. Pediatrics 2006; 117:e743–e750.
30. Baker KS, Filipovich AH, Gross TG, et al. Unrelated donor hematopoietic cell transplantation for hemophagocytic lymphohistiocytosis. Bone Marrow Transplant 2008;42:175–180.
31. Cooper N, Rao K, Gilmour K, et al. Stem cell transplantation with reduced-intensity conditioning for hemophagocytic lymphohistiocytosis. Blood 2006;107:1233–1236.
32. Cesaro S, Locatelli F, Lanino E, et al. Hematopoietic stem cell transplantation for hemophagocytic lymphohistiocytosis: A retrospective analysis of data from the Italian Association of Pediatric Hematology Oncology (AIEOP). Haematologica 2008;93:1694–1701.
33. Dürken M, Horstmann M, Bieling P, et al. Improved outcome in haemophagocytic lymphohistiocytosis after bone marrow transplantation from related and unrelated donors: A single-centre experience of 12 patients. Br J Haematol 1999;106:1052–1058.
34. Moshous D, Feyen O, Lankisch P, et al. Primary necrotizing lymphocytic central nervous system vasculitis due to perforin deficiency in a four-year-old girl. Arthritis Rheum 2007;56:995–999.
35. Horne A, Trottestam H, Aricò M, et al. Frequency and spectrum of central nervous system involvement in 193 children with haemophagocytic lymphohistiocytosis. Br J Haematol 2008;140: 327–335.
36. Gonzalez-Llano O, Jaime-Pérez J, Cantu-Rodríguez O, et al. Successful father-to-son stem cell transplantation in a child with hemophagocytic lymphohistiocytosis using a reduced-intensity conditioning regimen. Eur J Haematol 2006;77:341–344.
37. Jordan MB, Filipovich AH. Hematopoietic cell transplantation for hemophagocytic lymphohistiocytosis: A journey of a thousand miles begins with a single (big) step. Bone Marrow Transplant 2008;42:433–437.
38. Imashuku S, Teramura T, Tauchi H, et al. Longitudinal follow-up of patients with Epstein-Barr virus-associated hemophagocytic lymphohistiocytosis. Haematologica 2004;89:183–188.
39. Sato E, Ohga S, Kuroda H, et al. Allogeneic hematopoietic stem cell transplantation for Epstein-Barr virus-associated T/natural killer-cell lymphoproliferative disease in Japan. Am J Hematol 2008;83:721–727.
40. Han AR, Lee HR, Park BB, et al. Lymphoma-associated hemophagocytic syndrome: Clinical features and treatment outcome. Ann Hematol 2007;86:493–498.
41. Arkwright PD, Abinun M, Cant AJ. Autoimmunity in human primary immunodeficiency diseases. Blood 2002;99:2694–2702.
42. Brinkman DM, Jol-van der Zijde CM, ten Dam MM, et al. Resetting the adaptive immune system after autologous stem cell transplantation: Lessons from responses to vaccines. J Clin Immunol 2007;27:647–658.
43. Chen CJ, Ho TY, Lu JJ, et al. Identical twin brothers concordant for Langerhans' cell histiocytosis and discordant for Epstein-Barr virus-associated haemophagocytic syndrome. Eur J Pediatr 2004; 163:536–539.

Pediatr Blood Cancer 2010;54:98–102

Nationwide Survey of Single-System Single Site Langerhans Cell Histiocytosis in Japan

Akira Morimoto, MD,[1]* Yasushi Ishida, MD,[2] Nobuhiro Suzuki, MD,[3] Shouichi Ohga, MD,[4] Yoko Shioda, MD,[5] Yuri Okimoto, MD,[6] Kazuko Kudo, MD,[7] Eiichi Ishii, MD[8] and HLH/LCH Committee of the Japanese Society of Pediatric Hematology

Background. Since neither a standard treatment nor a protocol study for single-system single site (SS-s)-type Langerhans cell histiocytosis (LCH) exists, we conducted a nationwide survey in Japan to clarify the epidemiology and clinical outcome of this subtype. ***Procedure.*** Questionnaires regarding the clinical course of children with SS-s-type LCH diagnosed between 1995 and 2006 were sent to all members of the Japanese Society of Pediatric Hematology. ***Results.*** One hundred forty-six children with histologically proven SS-s LCH were evaluable. The most frequently affected organ was bone (82%), followed by skin (12%). Few patients (14%) had a CNS-RISK lesion defined by the Histiocyte Society. Patients with a skin lesion were diagnosed at a significantly younger age than patients with a bone lesion (median: 6 months vs. 5 years 11 months, $P < 0.001$). The treatment regimen varied, but one-third of the patients in total and 71% of patients with a CNS-RISK lesion received chemotherapy that did not include etoposide. All but one patient attained remission. Ten patients (7%) showed reactivation. Of these, all eight with an initial bone lesion only exhibited reactivation in the bone(s). One patient with an initial skin lesion exhibited reactivation in the thymus. None of the patients died from disease progression or treatment complications. ***Conclusions.*** Our retrospective study, in which a relatively large proportion of the patients received chemotherapy, reveals that patients with SS-s LCH have a good prognosis. A prospective study should be conducted to confirm this and to identify the most effective and least toxic therapy for SS-s LCH. Pediatr Blood Cancer 2010;54:98–102.

Key words: chemotherapy; epidemiology; Langerhans' cell histiocytosis; single system

INTRODUCTION

Langerhans cell histiocytosis (LCH) is the most common histiocytic disorder characterized by the uncontrolled clonal proliferation of Langerhans cells. Its clinical manifestations and course are highly variable, and range from a self-healing solitary lesion to fatal multiorgan involvement [1]. LCH is classified into three distinct forms: single-system single site (SS-s), single-system multisites (SS-m), and multisystem (MS) type. An epidemiological study in Japan [2] has reported that the SS-s, SS-m, and MS types of LCH are diagnosed at a ratio of almost 1:1:1.

Several clinical studies have been performed to improve the outcome of LCH. These include international clinical trials run by the Histiocyte Society [3,4] and a Japanese clinical study performed by the Japan LCH Study Group (JLSG) [5]. These studies have improved the outcome of SS-m and MS-type LCH. However, in terms of SS-s-type LCH, a standard treatment or a protocol study for it is lacking [6]. To date, only one study has examined a large number of patients with single-system LCH, namely, the prospective observational study denoted as DAL-HX 83/90 [7]. Because it appears that the prognosis of patients with SS-s-type LCH is generally good, it is less common that chemotherapy is applied to them [6]. However, the patients with the craniofacial bone(s) (orbital, temporal, mastoid, sphenoidal, zygomatical, ethomoidal bones, the maxilla, paranasal sinuses, or anterior or middle cranial fossa) with intracranial soft tissue extension (the so-called CNS-RISK lesion(s)) had higher risk for the development of diabetes insipidus (DI) [8], and the LCH-III protocol study conducted by the Histiocyte Society suggests that chemotherapy should be offered to these patients, even if there is only a single lesion [9].

To further clarify the epidemiology, clinical outcome of SS-s-type LCH, we conducted a nationwide survey of LCH in Japan. We found that the rates of reactivation and sequelae were remarkably low in our cohort of SS-s LCH, in which a relatively large proportion of the patients received chemotherapy.

DOI 10.1002/pbc.22224
Published online 2 September 2009 in Wiley InterScience (www.interscience.wiley.com)

MATERIALS AND METHODS

Data Collection

To compile the clinical data of new pediatric patients (age younger than 18 years at the time of diagnosis) with SS-s-type LCH who were diagnosed and treated between 1995 and 2006, the HLH/LCH Committee of the Japanese Society of Pediatric Hematology (JSPH) sent questionnaires to all the hospitals in Japan in which pediatric hematologists (JSPH members) worked. The SS-s type of LCH was defined as the infiltration of LCH cells in one site of one affected organ, as confirmed by histology. The questionnaire asked about the diagnostic procedure, the age at diagnosis, the sex, the site of the lesion, the treatment, the occurrence of complications, and the outcome. We received replies from 294 of 320 hospitals (92%). Eventually, the details of 174 patients from 81 hospitals were

[1]Department of Pediatrics, Jichi Medical University School of Medicine, Shimotsuke, Japan; [2]Division of Pediatrics, St. Luke's International Hospital, Tokyo, Japan; [3]Department of Pediatrics, Sapporo Medical University School of Medicine, Sapporo, Japan; [4]Department of Pediatrics, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan; [5]Division of Pediatric Oncology, National Center for Child Health and Development, Tokyo, Japan; [6]Division of Hematology Oncology, Chiba Children's Hospital, Chiba, Japan; [7]Department of Pediatrics, Institute of Clinical Medicine, University of Tsukuba, Tsukuba, Japan; [8]Department of Pediatrics, Graduate School of Medicine, Ehime University, Toon, Japan

The authors all state that there is no potential conflicts of interest.

Grant sponsor: Ministry of Health, Labor and Welfare, Japan.

*Correspondence to: Akira Morimoto, Department of Pediatrics, Jichi Medical University School of Medicine, 3311-1, Yakushiji, Shimotsuke, Tochigi 329-0498, Japan. E-mail: akira@jichi.ac.jp

Received 19 January 2009; Accepted 2 July 2009

complied. Of these, 28 patients were excluded from this study for following reasons: 5 because they had multisystem-type disease, 7 because they had multifocal bone type disease, and 16 because the diagnosis was not confirmed by biopsy and histology.

Statistical Analysis

The age of diagnosis of the patients was compared by using the Mann–Whitney *U*-test. In patients with bone lesion, the therapeutic modality and the factors affecting reactivation including gender, age at diagnosis, the region affected at onset, and type of initial treatment were analyzed by using the chi-square test. *P*-values less than 0.05 were considered significant.

RESULTS

One hundred forty-six patients with SS-s LCH from 71 hospitals were evaluable. The median observation time was 3.3 years. The diagnosis was based on the presence in the lesional cells of CD1a antigen and/or Birbeck granules (98 patients), langerin antigen (1 patient), and S100 protein (31 patients), or the hematoxylin–eosin staining findings (16 patients). There were 77 males and 69 females (Table I). The median age at diagnosis was 4.8 years, ranging from 0.0 to 16.8 years. The most frequently affected organ was bone (120 patients, 82%), followed by skin (18 patients, 12%). The site of the bone lesion was a CNS-RISK in 21 patients, the skull or facial bone other than a CNS-RISK lesion in 49, the vertebra in 8, the extremities in 26, the pelvis in 5, and the thorax in 11. The age of diagnosis of the patients with a CNS-RISK lesion was significantly lower than that with other bone lesions (median age: 3 years 7 months vs. 6 years 3 months, $P = 0.021$). Of the patients with a skin lesion, 61% were less than 1 year old and were significantly younger than those with a bone lesion (median age: 6 months vs. 5 years 11 months, $P < 0.001$). The patients with a bone lesion were more frequently male (male/female ratio: 1.22), especially in those with a lesion on an extremity (ratio: 2.25). In contrast, neither gender was more likely to have a skin lesion.

Of the patients with a bone lesion, 33% were treated with chemotherapy, 35% were treated with curettage, and 23% received a biopsy only. More than 70% in the patients with a CNS-RISK lesion and nearly two-third of patients with vertebral bone lesion received chemotherapy. The frequency of receiving chemotherapy in patients with a CNS-RISK lesion was significantly high compared to in patients with other bone lesions (15/21 vs. 24/99, $P < 0.001$).

Of the patients with a skin lesion, 28% were treated with chemotherapy, while 56% were treated with biopsy only and remaining patients received surgical treatment or corticosteroid therapy (Table II). Although the chemotherapy regimen used varied, none of the patients received etoposide. All but 1 patient (99%) attained remission, but 10 patients (7%) subsequently suffered a reactivation. None of the patients died of disease progression or treatment complications. At last follow-up, 144 of 146 (99%) did not have active disease (Table II).

All eight patients with reactivated disease and an initial bone lesion exhibited a skeletal reactivation only (two in the same site at onset, one in another site, and five in multiple sites). Of the two reactivated patients with an initial skin lesion, the reactivation occurred in the skin in one and in the thymus in the other. The median duration from diagnosis to reactivation was 4 months (range, 0.1–2.5 years) (Table III). Any factors including gender, age at diagnosis, the region affected at onset, and the type of initial treatment were not associated with reactivation of LCH involving a single bone in this analysis (Table IV).

Six patients (4%) had late sequelae. Four with an initial bone lesion had orthopedic sequelae. Two patients suffered developmental impairments: one patient with a thymus lesion had a developmental impairment due to hypoxia arising from airway obstruction, while the other patient, who had a lesion on the intracranial mass, had a developmental impairment because of damage during surgery. None of the patients had DI. There was no correlation between reactivation and the sequelae (Table III).

TABLE I. Characteristics of Patients With SS-s LCH

Site involved	n (%)	Gender (M/F)	Age at diagnosis (median)
Bone	120 (82)	66/54	5m to 16y 9m (5y 11m)
CNS-RISK lesion[a]	21 (14)	14/7	6m to 14y0m (3y7m)*
Non CNS-RISK lesion[b]	49 (34)	26/23	10m to 16y0m (7y4m)
Extremities	26 (18)	18/8	5m to 15y3m (4y5m)
Thorax/shoulder	11 (8)	1/10	1y7m to 9y8m (5y0m)
Vertebra	8 (5)	5/3	11m to 16y9m (11y2m)
Pelvis	5 (3)	2/3	2y6m to 13y2m (7y0m)
Skin	18 (12)	9/9	0m to 14y1m (6m)[#]
Soft tissue	2 (1)	1/1	3m and 4y3m
Oral mucosa	2 (1)	1/1	1m and 6y7m
Thymus	2 (1)	0/2	5m and 3y0m
Lymph node	1 (1)	0/1	1y6m
Intra cranial mass	1 (1)	0/1	1m
Total	146 (100)	77/69	0m to 16y9m (4y10m)

m, months; y, years. [a]Combined lesions in the orbital, temporal, mastoid, sphenoidal, zygomatical, ethomoidal bones, the maxilla, paranasal sinuses, or anterior or middle cranial fossa, with intracranial soft tissue extension; [b]Skull or facial bone lesion other than CNS-RISK lesion; *Significantly young compared to patients with other bone lesion ($P = 0.021$); [#]Significantly young compared to patients with the bone lesion ($P < 0.001$).

TABLE II. Initial Treatment and Outcome of SS-s LCH (n (%))

Site involved		Initial treatment					Outcome			
				Corticosteroid					Status at last follow-up		
		None	Curettage / resection	Local	Systemic	Radiation	Chemotherapy	Attained remission	Subsequent reactivation	NAD	AD	Sequelae
Bone	120	27 (23)	42 (35)	7 (6)	4 (3)	1 (1)	39 (33)	120 (100)	8 (7)	119 (99)	1 (1)	4 (3)
CSN-RISK lesion[a]	21	2 (10)	3 (14)	0	1 (5)	0	15 (71[#])	21 (100)	1 (5)	21 (100)	0	0
Non CNS-RISK lesion[b]	49	8 (16)	28 (57)	0	1 (2)	1 (2)	11 (22)	49 (100)	3 (6)	49 (100)	0	2 (4)
Extremities	26	11 (42)	5 (19)	3 (12)	1 (4)	0	6[c] (23)	26 (100)	2 (8)	26 (100)	0	1 (4)
Thorax/shoulder	11	3 (27)	4 (36)	2 (18)	1 (9)	0	1 (9)	11 (100)	2 (18)	10 (91)	1 (9)	0
Vertebra	8	1 (13)	0	2 (25)	0	0	5[c] (63)	8 (100)	0	8 (100)	0	1 (13)
Pelvis	5	2 (40)	2 (40)	0	0	0	1 (20)	5 (100)	0	5 (100)	0	0
Skin	18	10 (56)	1 (6)	1 (6)	1 (6)	0	5 (28)	17 (94)	2 (11)	17 (94)	1 (6)	0
Other	8	0	4 (50)	0	0	0	4 (50)	8 (100)	0	8 (100)	0	2 (25)
Total	146	37 (25)	47 (32)	8 (5)	5 (3)	1 (1)	48 (33)	145 (99)	10 (7)	144 (99)	2 (1)	6 (4)

NAD, no active disease; AD, active disease. [a]Combined lesions in the orbital, temporal, mastoid, sphenoidal, zygomatical, ethomoidal bones, the maxilla, paranasal sinuses, or anterior or middle cranial fossa, with intracranial soft tissue extension; [b]Skull or facial bone lesion other than CNS-RISK lesion; [c]Including one patient received treatment combined chemotherapy and radiation; [#]Significantly high incidence compared to patients with the other bone lesion ($P < 0.001$).

DISCUSSION

In this study, we retrospectively analyzed 146 patients with SS-s LCH. Although the pediatric hematologists in over 90% of the hospitals in Japan answered the questionnaire we sent, it remains possible that some patients were excluded because they were under the care of an orthopedist or dermatologist.

In our cohort, the organ that was most frequently affected was bone (over 80% of the patients had a lesion in bone), followed by skin. The patients with a skin lesion were younger than those with a bone lesion, while males developed SS-s LCH more frequently than women. These features were quite similar to those of the cohort studied by the DAL-HX study [7]. They were also consistent with the results of an epidemiological study that found, of unifocal LCH patients, 70% had a bone lesion, 77% of the patients with a skin lesion were less than 1 year old, and males were more often affected by the disease than females (male/female ratio: 1.3) [10].

The involvement of CNS-RISK lesion(s) carry an about threefold risk for the development of DI which is the hallmark of central nervous system involvement in LCH [8]. Of patients enrolled onto DAL-HX83/90, LCH-I, and LCH-II, majority of whom were MS or SS-m-type LCH, 43% had CNS-RISK lesion(s) [8]. In our SS-s cohort, only 14% of patients had a CNS-RISK lesion, who were significantly younger than patients with other bone lesion. The frequency of the CNS-RISK lesion might rise as SS-s, SS-m, MS, and the disease stage progress.

We found one-third of the patients with a bone lesion were treated with chemotherapy. In particular, more than 70% of patients with a CNS-RISK lesion and nearly two-thirds of patients with a vertebral bone lesion received chemotherapy. A considerable proportion of the patients with a skin lesion (28%) also received chemotherapy. In the DAL-HX study [7], only 8% of patients with a single bone lesion were given systemic treatment. In the LCH-III protocol study chemotherapy is offered to patients with vertebral lesion(s) as well as CNS-RISK lesion(s), even if only a single lesion is present [9]. However, in general, few patients with unifocal bone lesion are treated with chemotherapy. Indeed, in one report from a neurosurgeon, only 3 of 27 (11%) patients with unifocal LCH in a craniospinal site were treated [11].

Regardless of the type of treatment, almost all patients attained remission, and none of the patients died of disease progression or treatment complications. Some patients suffered from reactivation, mostly within a year after diagnosis. In patients exhibiting reactivation, all with only an initial bone lesion showed reactivation in bone(s), whereas some patients with a skin lesion suffered a reactivation in areas other than skin and progressed to multisystem-type LCH. These features were also similar to those of the cohort described by the DAL-HX study [7]. As previously reported [12], isolated cutaneous LCH in infants may be an aggressive disorder that can progress to multiorgan involvement.

The rates of both reactivation and sequelae of LCH involving a single bone in our study were low compared to the rates reported in the DAL-HX study (8/120 vs. 22/121; $P = 0.007$, and 3/120 vs. 25/121; $P < 0.001$, respectively) [7]. Four of the 120 patients (3%) with a bone lesion suffered from orthopedic consequences and two patients with lesions in special areas other than the skin or bone suffered from developmental impairment. In contrast, the DAL-HX study reported that sequelae were already present at diagnosis in 10% of patients with a bone lesion, and that more than half of the sequelae involved orthopedic disabilities, followed by neurologic

TABLE III. Characteristics of the Patients Who Suffered a Reactivation or Sequelae

Initial site	Gender	Age at diagnosis	Initial treatment	Reactivation		Sequelae
				Site	Interval[a]	
Bone						
CNS-RISK lesion[b]	M	1y3m	Chemotherapy	Multiple bone	1y0m	None
Non-CNS-RISK lesion[c]	M	6y1m	Curettage	Multiple bone	3m	None
Non CNS-RISK lesion[c]	F	12y10m	Curettage	Single same bone	1y0m	None
Non-CNS-RISK lesion[c]	F	12y7m	Systemic steroid	Single same bone	1m	None
Upper limb	M	4y7m	None	Multiple bone	3m	None
Lower limb	M	2y5m	None	Multiple bone	2m	None
Thorax	F	7y1m	Curettage	Multiple bone	3m	None
Shoulder	F	7y5m	Chemotherapy	Single other bone	2y6m	None
Skin	M	5m	None	Thymus	5m	None
	F	6m	Chemotherapy	Skin	9m	None
Bone						
Non-CNS-RISK lesion[c]	M	12y5m	Curettage	None		Bone defect
Non-CNS-RISK lesion[c]	F	8y5m	Curettage	None		Bone defect
Lower limb	M	2y0m	Chemotherapy	None		Bone fracture
Vertebra	M	16y9m	Chemotherapy	None		Flat bone
Thymus	F	5m	Chemotherapy	None		DD
Cranial mass	F	1m	Resection	None		DD

DD, developmental disorder; m, months; y, years. [a]Interval from diagnosis; [b]Combined lesions in the orbital, temporal, mastoid, sphenoidal, zygomatical, ethomoidal bones, the maxilla, paranasal sinuses, or anterior or middle cranial fossa, with intracranial soft tissue extension; [c]Skull or facial bone lesion other than CNS-RISK lesion.

consequences, and DI and/or anterior pituitary dysfunction. A retrospective study from Argentina had similar results as the DAL-HX study: of 161 patients with single-system unifocal LCH, reactivation occurred in 17.4%, and sequelae, mainly orthopedic problems, developed in 19.1% (the mean follow-up time was 4.8 years) [13]. However, this study did not include information on the type of treatment which these patients received [13].

No factor associated with reactivation of LCH involving a single bone was found in this analysis. We speculate that the low rate of patients with a CNS-RISK lesion, who have intrinsically high risk of DI, and the high rate of applying chemotherapy to these patients in our cohort could be responsible for this as well as the low rates of reactivation and sequelae in our cohort. Most reactivations occurred within 1 year from diagnosis in our study, which suggests that the observation time (median 3.3 years) is sufficient for determining the reactivation rate of our cohort. However, the observation time in our study is too short to draw conclusions with regard to the sequelae rate, because while DI usually developed within 3 years after diagnosis, the rates of neurological consequences increased rapidly 10 years after diagnosis, and the incidence of orthopedic abnormalities and growth retardation accrued with each passing year after diagnosis [14].

In conclusion, we conducted a retrospective study of patients with SS-s LCH in Japan and found that a relatively large proportion received chemotherapy and that the prognosis was generally good. A prospective study should be conducted to confirm these results and to identify the most effective and least toxic therapy for SS-s LCH.

TABLE IV. Factors Affecting Reactivation in Patients With a Bone Lesion

Variables	Reactivation	*P*-value
Gender		
Male	4/66	
Female	4/54	0.769
Age at diagnosis[a]		
<6 years old	3/59	
>6 years old	5/59	0.464
Region		
CNS-RISK lesion[b]	1/21	
Other than CNS-RSK lesion	7/99	0.700
Treatment		
Chemotherapy	2/39	
Other than chemotherapy	6/81	0.639

[a]Data of age at diagnosis were missing in two patients; [b]Combined lesions in the orbital, temporal, mastoid, sphenoidal, zygomatical, ethomoidal bones, the maxilla, paranasal sinuses, or anterior, or middle cranial fossa, with intracranial soft tissue extension.

Pediatr Blood Cancer DOI 10.1002/pbc

ACKNOWLEDGMENT

The authors thank the physicians who participated in this study. This work was supported by a Grant for Research on Measures for Intractable Diseases from the Ministry of Health, Labor and Welfare, Japan.

REFERENCES

1. Henter JI, Tondini C, Pritchard J. Histiocyte disorders. Crit Rev Oncol Hematol 2004;50:157–174.
2. Imashuku S, Ikushima S, Hibi S, et al. Langerhans cell histiocytosis and hemophagocytic syndrome in Japan; epidemiological studies. Int J Hematol Oncol 1994;1:241–246.
3. Gadner H, Grois N, Arico M, et al. A randomized trial of treatment for multisystem Langerhans' cell histiocytosis. J Pediatr 2001;138: 728–734.

4. Gadner H, Grois N, Pötschger U, et al. Improved outcome in multisystem Langerhans cell histiocytosis is associated with therapy intensification. Blood 2008;111:2556–2562.
5. Morimoto A, Ikushima S, Kinugawa N, et al. Improved outcome in the treatment of pediatric multifocal Langerhans cell histiocytosis: Results from the Japan Langerhans Cell Histiocytosis Study Group-96 protocol study. Cancer 2006;107:613–619.
6. Gadner H, Ladisch S. The treatment of Langerhans cell histiocytosis. In: Weitzman S, Egeler RM, editors. Histiocytic disorders of children and adults. Cambridge: Cambridge University Press; 2005. pp. 229–253.
7. Titgemeyer C, Grois N, Minkov M, et al. Pattern and course of single-system disease in Langerhans cell histiocytosis data from the DAL-HX 83- and 90-study. Med Pediatr Oncol 2001;37:108–114.
8. Grois N, Pötschger U, Prosch H, et al. Risk factors for diabetes insipidus in Langerhans cell histiocytosis. Pediatr Blood Cancer 2006;46:228–233.
9. McClain KL. Drug therapy for the treatment of Langerhans cell histiocytosis. Expert Opin Pharmacother 2005;6:2435–2441.
10. Guyot-Goubin A, Donadieu J, Barkaoui M, et al. Descriptive epidemiology of childhood Langerhans cell histiocytosis in France, 2000–2004. Pediatr Blood Cancer 2008;51:71–75.
11. Davidson L, McComb JG, Bowen I, et al. Craniospinal Langerhans cell histiocytosis in children: 30 years' experience at a single institution. J Neurosurg Pediatr 2008;1:187–195.
12. Lau L, Krafchik B, Trebo MM, et al. Cutaneous Langerhans cell histiocytosis in children under one year. Pediatr Blood Cancer 2006;46:66–71.
13. Pollono D, Rey G, Latella A, et al. Reactivation and risk of sequelae in Langerhans cell histiocytosis. Pediatr Blood Cancer 2007;48:696–699.
14. Haupt R, Nanduri V, Calevo MG, et al. Permanent consequences in Langerhans cell histiocytosis patients: A pilot study from the Histiocyte Society-Late Effects Study Group. Pediatr Blood Cancer 2004;42:438–444.

Characteristics of Hemophagocytic Lymphohistiocytosis in Neonates: A Nationwide Survey in Japan

Nobuhiro Suzuki, MD, PHD, Akira Morimoto, MD, PHD, Shouichi Ohga, MD, PHD, Kazuko Kudo, MD, PHD, Yasushi Ishida, MD, PHD, and Eiichi Ishii, MD, PHD, for the HLH/LCH Committee of the Japanese Society of Pediatric Hematology*

Objective To assess the etiology, prognosis, and appropriate treatment of hemophagocytic lymphohistiocytosis (HLH) in neonates.

Study design We collected information on neonates in whom HLH was diagnosed between 1997 and 2007 from participating members of the Japanese Society of Pediatric Hematology.

Results HLH was diagnosed in 20 patients within 4 weeks after birth. Of the diagnostic criteria for HLH-2004, the incidence of fever was quite low in preterm infants, and hypertriglyceridemia and neutropenia were uncommon. Familial HLH (n = 6) or severe combined immunodeficiency-associated HLH (n = 1) was diagnosed in 7 patients, and 2 of them have survived. Herpes simplex virus-associated HLH was diagnosed in 6 patients, and 2 of them have survived. The overall survival rate for the 20 patients was 40%.

Conclusions HLH is rare in neonates and has a poor prognosis. Early diagnosis and immediate treatment are required when considering the possibility of herpes simplex virus-associated or familial HLH. *(J Pediatr 2009;155:235-8).*

Hemophagocytic lymphohistiocytosis (HLH) comprises a heterogeneous class of often fatal disorders characterized by activation and disregulation of T-cells and macrophages.[1] The central role played by CD8 T cell activation, interferon overproduction, and macrophage activation in the pathophysiology of the disease was demonstrated in perforin-deficient mice.[2] HLH encompasses several entities, including a primary form that may be familial HLH, with an estimated incidence of 1 in 50 000 births,[3] and a secondary form associated with infections, malignancies, and rheumatologic disorders.[4]

Neonatal HLH with an onset within 4 weeks after birth is rare, and the diagnosis is frequently delayed, made only at autopsy or missed completely. Speculating that neonatal HLH might differ from HLH in older children in etiology, manifestations, or laboratory findings, we conducted this nationwide Japanese survey of cases of neonatal HLH to clarify the etiology and prognosis. On the basis of the findings, we propose an appropriate strategy for diagnosis and treatment.

Methods

Clinical and laboratory findings at the onset, treatment, and outcome were analyzed in neonates in whom HLH was diagnosed at ≤4 weeks after birth between 1997 and 2007. Data were collected from participating members of the Japanese Society of Pediatric Hematology. The diagnosis of HLH was mainly based on the HLH-2004 criteria (Table I).[5] Patients whose laboratory data did not fulfill the HLH-2004 criteria were also included when they had a family history of HLH or hemophagocytosis in the peripheral blood.[6] All aspects of this investigation were approved by the appropriate institutional review boards.

Results

HLH was diagnosed in 20 neonates (10 male, 10 female; Table II). The day of onset was from 0 to 28 days after birth (median, 6.5 days); HLH was diagnosed in 6 patients at birth. Eight patients were preterm, <37 weeks gestational age.

Clinical and biological findings are summarized in Figure 1. Fever was noted in only 1 of the 8 preterm infants (12.5%), compared with 10 of the 12 term infants (83.3%). Hypertriglyceridemia and neutropenia were

β2-MG	beta-2-microglobulin
CSF	Cerebrospinal fluid
HLH	Hemophagocytic lymphohistiocytosis
HSV	Herpes simplex virus
LDH	Lactate dehydrogenase
SCID	Severe combined immunodeficiency
sIL-2R	Soluble interleukin-2 receptor

From the Department of Pediatrics, Sapporo Medical University School of Medicine (N.S.), Sapporo, Japan; Department of Pediatrics, Jichi Medical University School of Medicine (A.M.), Shimotsuke, Japan; Department of Pediatrics, Kyushu University Faculty of Medicine (S.O.), Fukuoka, Japan; Department of Pediatrics, Institute of Clinical Medicine, University of Tsukuba (K.K.), Tsukuba, Japan; Department of Pediatrics, St. Luke's International Hospital (Y.I.), Tokyo, Japan; and Department of Pediatrics, Ehime University Graduate School of Medicine (E.I.), Toon, Japan

*A list of hospitals that enrolled patient(s) in this study appears in the Appendix (available at www.jpeds.com).

The authors declare no real or perceived conflicts of interest.

 10.1016/j.jpeds.2009.02.050

Table I. **Diagnostic guidelines for hemophagocytic lymphohistiocytosis**

The diagnosis of HLH can be established when 1 of either 1 or 2 below is fulfilled:
1) A molecular diagnosis consistent with HLH
2) Diagnostic criteria for HLH fulfilled (5 of the 8 criteria below)
Fever
Splenomegaly
Cytopenias (affecting ≥ 2 of 3 lineages in the peripheral blood):
Hemoglobin <100 g/L
Platelets <100 x 10^9/L
Neutrophils <1.0 x 10^9/L
Hypertriglyceridemia and/or hypofibrinogenemia:
Fasting triglycerides ≥3.0 mmol/L (ie, ≥265 mg/dL)
Fibrinogen ≤1.5 g/L
Hemophagocytosis in bone marrow or spleen or lymph nodes.
No evidence of malignancy
Low or absent NK-cell activity (according to local laboratory reference)
Ferritin ≥500 microgram/L
Soluble CD25 (ie, soluble IL-2 receptor ≥ 2400 U/mL)

infrequent. Respiratory distress was noted in 15 patients at birth, including all 8 preterm infants. Nineteen patients had an elevated lactate dehydrogenase (LDH) level. The urinary beta-2-microglobulin (β2-MG) level was elevated to >1 000 μg/L (range, 3.33-96 630 μg/L; median, 3 900 μg/L) in 8 of the 11 patients examined (72.7%). Of the 6 patients who had the disease at birth, fetal distress had been diagnosed in 4 before delivery. Hydrops fetalis was present in 1 patient (patient 8). Two patients had skin manifestations, erythema in patient 4 and a dusky-red papular rash in patient 19. Abnormal results on magnetic resonance imaging of the brain were recorded in 3 patients with clinical manifestations of impaired consciousness (patient 6), seizure (patient 11), or ocular deviation (patient 9). The cerebrospinal fluid (CSF) was examined in 10 patients, and results were abnormal in 2 cases, with a polymorphonuclear cell dominant pleocytosis in patient 6 and a raised protein level but a normal white blood cell count and impaired consciousness in patient 8.

Six patients (30%) were considered to have familial HLH. Severe combined immunodeficiency (SCID)-associated HLH was diagnosed in 1 patient. Herpes simplex virus (HSV)-associated HLH was noted in 6 patients (30%). The other 7 patients had HLH associated with cytomegalovirus, coxsackievirus, methicillin-resistant *Staphylococcus aureus*, or cause unknown.

Patients were treated with corticosteroid (n = 17, 85%), intravenous gamma globulin (n = 15, 75%), exchange transfusion/plasma exchange (n = 12, 60%), and cyclosporine, etoposide, or acyclovir (n = 8-9, 40%-45%; Table II). Three patients with familial HLH-3 (UNC13D deficiency), SCID-HLH, and unknown cause-HLH underwent subsequent hematopoetic stem cell transplantation.

Eight of the 20 patients survived (40%). Of the 7 patients with familial HLH or SCID-HLH, only 2 (28.6%) have survived (Figure 2), and of 6 patients with HSV-HLH, only 2 (33.3%) survived, despite receiving acyclovir. No significant statistical differences were found between the 8 survivors and the 12 non-survivors in their laboratory findings, including aspartate aminotransferase, LDH, ferritin, soluble IL-2 receptor (sIL-2R), and fibrinogen (data not shown).

Table II. **Patient characteristics**

n	Sex	GA (weeks)	Onset (days after birth)	Matched numbers of HLH-2004 diagnostic criteria	Type of HLH	Therapy	Outcome
1[21]	M	23	17	5/6	CMV	γ, S	Dead 73d
2	F	27	0	4/5	FHL*	γ, S	Dead 2 m 18d
3	F	29	7	2/5	HSV	γ	Dead 10d
4	M	30	0	6/7	FHL*	S, C, Et	Alive 7m+ (with disease)
5[22]	M	31	0	6/8	FHL*	S	Dead 42d
6	F	33	11	5/8	COX	E	Alive 1y 9m+
7	F	36	0	5/7	unknown	γ, S, E, HSCT	Alive 9y 4 m
8[23]	M	36	0	6/8	FHL-3	γ, S, C, Et, P, CA	Dead 114d
9	F	37	14	7/8	unknown	γ, S, Et, ACV	Alive 5y 11m+
10	F	38	5	7/8	HSV	γ, S, C, Et, ACV	Dead 27d
11	M	39	3	6/8	HSV	γ, S, C, Et, P, ACV	Dead 61d
12	F	39	0	6/8	unknown	γ, S, C, Et, E	Dead 35d
13[24]	M	39	4	5/7	HSV	γ, S, C, E, ACV	Alive 1y 10m+
14	F	39	28	6/7	unknown	S, Et, E	Dead 38d
15	M	39	8	5/7	HSV	γ, S, C, E, ACV	Alive 2y 6m+
16	M	39	24	7/7	FHL-3	γ, S, C, HSCT	Alive 1y 6m+
17	M	39	17	5/6	FHL-2	γ, S, E, ACV	Dead 29d
18	F	40	6	6/6	HSV	γ, S, E, ACV	Dead 29d
19	F	41	19	5/8	SCID	γ, S, C, Et, E, ACV, HSCT	Dead 2 m 27d
20	M	41	17	5/8	MRSA	antibiotics	Alive 7y 7m+

M, Male; *F*, female; *CMV*, cytomegalovirus; *FHL*, Familial hemophagocytic lymphohistiocytosis; *HSV*, herpes simplex virus; *COX*, coxsackievirus; *SCID*, severe combined immunodeficiency disease; *MRSA*, methicillin-resistant *Staphylococcus aureus*; γ, gamma globulin; *S*, corticosteroid; *C*, cyclosporine; *Et*, etoposide; *E*, exchange transfusion; *HSCT*, hematopoietic stem cell transplantation; *P*, plasma exchange; *CA*, cytosine arabinoside; *ACV*, acyclovir; *d*, days; *m*, month(s); *y*, year(s).
*FHL of unknown genetic defects with positive family history.

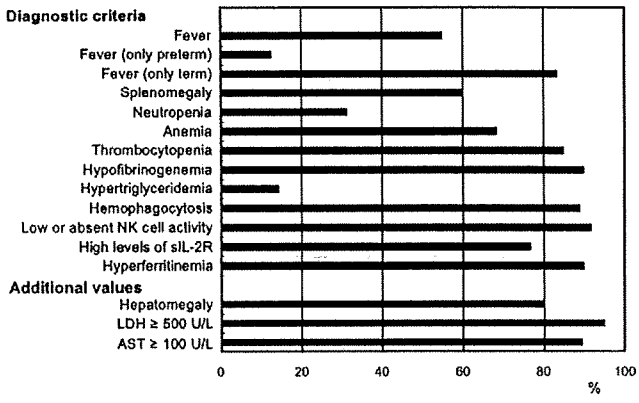

Figure 1. Incidence of clinical and biochemical findings of 20 patients with neonatal hemophagocytic lymphohistiocytosis. Of the usual diagnostic features, neutropenia and hypertriglyceridemia were low, and the incidence of fever was low in the preterm neonates.

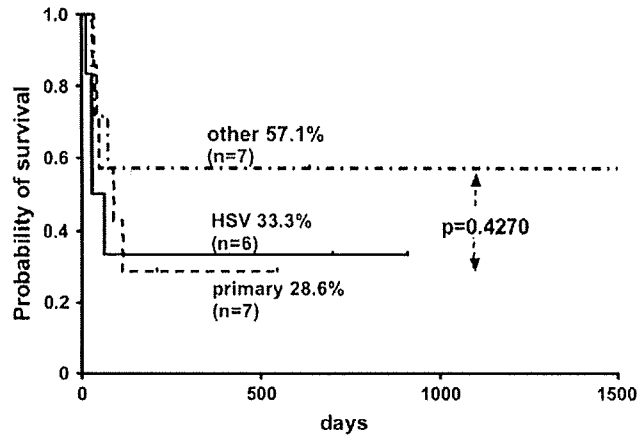

Figure 2. Outcome of patients with HLH according to the etiology. The 5-year overall survival rate of primary HLH (familial and severe combined immunodeficiency-associated HLH) and HSV-associated HLH was poor compared with that of other HLH, although no significant difference was observed in the 3 groups.

Discussion

Most reports of HLH in neonates have been included in childhood HLH studies.[7,8] Consequently, the characteristics of neonatal HLH have not been well defined. In a recent study of infantile HLH, the 9 cases of neonatal HLH had a poor prognosis, 2 of the 9 cases with familial HLH developed disease at birth and 7 patients with HSV-HLH or enterovirus-associated HLH presented between 4 and 13 days after birth.[9] Although HSV and enterovirus are uncommon pathogens in HLH in older children, they have been reported as causes of severe HLH in neonates.[6,10-12] In this study, 30% of the cases were diagnosed as HSV-HLH, with a poor prognosis.

The onset of familial HLH occurs at <1 year of age in 70% to 80% of the cases, and only approximately 10% of patients had symptoms within the neonatal period.[13] However, our study and an earlier report revealed that at least 30% of neonatal HLH could be classified as familial HLH.[9] In most cases of familial HLH, immunochemotherapy can temporarily control the disease, but the disease is eventually fatal unless hematopoetic stem cell transplantation is performed.[14] Considering that at least 60% of neonatal HLH is HSV-HLH or familial HLH, the appropriate treatment is high-dose acyclovir[11] followed by immunotherapy started immediately after making the diagnosis and surveying for pathogens.

Because fever seldom developed in the preterm infants in this study, HLH enters the differential diagnosis in preterm infants even when fever is absent. Most older children with HLH have hypertriglyceridemia,[15] which was found in only 14.3% of our patients. This difference may reflect the different metabolism of lipids in neonates compared with older patients.[16]

Neonatal hemochromatosis is sometimes indistinguishable from neonatal HLH. A ferritin level exceeding 10 000 mg/L has a high specificity and sensitivity for HLH,[17] and fever, cytopenias, and hypertriglyceridemia are not observed in patients with neonatal hemochromatosis.[18,19] However, these findings are not always useful for differentiating the 2 conditions in neonates. Evaluation of hemophagocytosis, natural killer cell activation, and sIL-2R may help. Urinary β2-MG is also a useful marker for HLH.[20]

In conclusion, the incidence of clinical and laboratory findings of neonatal HLH differ from those of childhood HLH. Neonates with hepatomegaly, thrombocytopenia, and elevated LDH levels should be further examined to exclude HLH. Once HLH is suspected, viral studies, levels of urinary β2-MG, sIL-2R, and natural killer cell activity, and an examination for hemophagocytosis in the bone marrow should be performed. Simultaneously, prompt treatment with combined high-dose acyclovir, gamma globulin, and cyclosporine with or without corticosteroid should be instituted. Etoposide should be used immediately after recognizing inadequate control of the disease by the initial immunotherapy. In familial cases, subsequent pregnancies and offspring should be closely monitored. ■

The authors thank the physicians who participated in this study. We also thank Dr Peter Olley (Professor Emeritus, University of Alberta, Canada) for help with the manuscript preparation.

Submitted for publication Nov 3, 2008; last revision received Dec 30, 2008; accepted Feb 26, 2009.

Reprint requests: Nobuhiro Suzuki, M.D., PH.D., Department of Pediatrics, Sapporo Medical University School of Medicine, S-1, W-16, Chuo-ku, Sapporo, 060-8543 Japan. E-mail: nsuzuki@sapmed.ac.jp.

References

1. Ishii E, Ohga S, Tanimura M, Imashuku S, Sako M, Mizutani S, et al. Clinical and epidemiologic studies of familial hemophagocytic lymphohistiocytosis in Japan. Japan LCH study group. Med Pediatr Oncol 1998; 30:276-83.

2. Jordan MB, Hildeman D, Kappler J, Marrack P. An animal model of hemophagocytic lymphohistiocytosis (HLH): CD8 + T cells and interferon gamma are essential for the disorder. Blood 2004;104: 735-43.
3. Henter JI, Elinder G, Soder O, Ost A. Incidence in Sweden and clinical features of familial hemophagocytic lymphohistiocytosis. Acta Paediatr Scand 1991;80:428-35.
4. Janka G, Imashuku S, Elinder G, Schneider M, Henter JI. Infection- and malignancy-associated hemophagocytic syndromes. secondary hemophagocytic lymphohistiocytosis. Hematol Oncol Clin North Am 1998;12: 435-44.
5. Henter JI, Horne A, Arico M, Egeler RM, Filipovich AH, Imashuku S, et al. HLH-2004: diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis. Pediatr Blood Cancer 2007;48:124-31.
6. Imashuku S, Tanaka T, Togari H, Teramura T, An B, Okubo H, et al. Detection of hemophagocytes in blood smears in fatal disseminated neonatal herpes simplex virus infection. Int J Pediatr Hematol/Oncol 2000;6: 425-8.
7. Arico M, Janka G, Fischer A, Henter JI, Blanche S, Elinder G, et al. Hemophagocytic lymphohistiocytosis. report of 122 children from the international registry. FHL study group of the histiocyte society. Leukemia 1996;10:197-203.
8. Isaacs H Jr. Fetal and neonatal histiocytoses. Pediatr Blood Cancer 2006; 47:123-9.
9. Imashuku S, Ueda I, Teramura T, Mori K, Morimoto A, Sako M, et al. Occurrence of haemophagocytic lymphohistiocytosis at less than 1 year of age: analysis of 96 patients. Eur J Pediatr 2005;164:315-9.
10. Abzug MJ. Prognosis for neonates with enterovirus hepatitis and coagulopathy. Pediatr Infect Dis J 2001;20:758-63.
11. Whitley R. Neonatal herpes simplex virus infection. Curr Opin Infect Dis 2004;17:243-6.
12. Rittichier KR, Bryan PA, Bassett KE, Taggart EW, Enriquez FR, Hillyard DR, et al. Diagnosis and outcomes of enterovirus infections in young infants. Pediatr Infect Dis J 2005;24:546-50.
13. Janka GE. Familial and acquired hemophagocytic lymphohistiocytosis. Eur J Pediatr 2007;166:95-109.
14. Henter JI, Samuelsson-Horne A, Arico M, Egeler RM, Elinder G, Filipovich AH, et al. Treatment of hemophagocytic lymphohistiocytosis with HLH-94 immunochemotherapy and bone marrow transplantation. Blood 2002;100:2367-73.
15. Mahlaoui N, Ouachee-Chardin M, de Saint Basile G, Neven B, Picard C, Blanche S, et al. Immunotherapy of familial hemophagocytic lymphohistiocytosis with antithymocyte globulins: a single-center retrospective report of 38 patients. Pediatrics 2007;120:e622-8.
16. Herrera E, Amusquivar E. Lipid metabolism in the fetus and the newborn. Diabetes Metab Res Rev 2000;16:202-10.
17. Allen CE, Yu X, Kozinetz CA, McClain KL. Highly elevated ferritin levels and the diagnosis of hemophagocytic lymphohistiocytosis. Pediatr Blood Cancer 2008;50:1227-35.
18. Parizhskaya M, Reyes J, Jaffe R. Hemophagocytic syndrome presenting as acute hepatic failure in two infants: clinical overlap with neonatal hemochromatosis. Pediatr Dev Pathol 1999;2:360-6.
19. Kapoor S. Distinguishing hemophagocytic lymphohistiocytosis from hemochromatosis in patients with hyperferritinemia. Pediatr Blood Cancer 2008;50:1287-8.
20. Hibi S, Ikushima S, Fujiwara F, Hashida T, Tsunamoto K, Todo S, et al. Serum and urine beta-2-microglobulin in hemophagocytic syndrome. Cancer 1995;75:1700-5.
21. Maruyama K, Koizumi T, Hirato J. Cytomegalovirus infections associated hemophagocytic lymphohistiocytosis in a premature infant. Pediatr Int 2006;48:648-50.
22. Nitta A, Suzumura H, Watabe Y, Okuya M, Nakajima D, Kurosawa H, et al. Fetal hemophagocytic lymphohistiocytosis in a premature infant. J Pediatr 2007;151:98.
23. Nakao T, Shimizu T, Fukushima T, Saito M, Okamoto M, Sugiura M, et al. Fatal sibling cases of familial hemophagocytic lymphohistiocytosis (FHL) with MUNC13-4 mutations: case reports. Pediatr Hematol Oncol 2008;25:171-80.
24. Yamada K, Yamamoto Y, Uchiyama A, Ito R, Aoki Y, Uchida Y, et al. Successful treatment of neonatal herpes simplex-type 1 infection complicated by hemophagocytic lymphohistiocytosis and acute liver failure. Tohoku J Exp Med 2008;214:1-5.

Appendix

List of hospitals that enrolled patient(s) in this study: Asahikawa-Kosei general Hospital; Chiba University Hospital; Dokkyo Medical University Hospital; Ehime University Hospital; Gifu Prefectural General Medical Center; Gunma Children's Medical Center; Hiroshima University Hospital; Jichi Medical University Hospital; Kanagawa Children's Medical Center; University Hospital, Kyoto Prefectural University of Medicine; Nippon Medical School Tama Nagayama Hospital; Sapporo Medical University Hospital; Tsukuba University Hospital; Wakayama Medical University Hospital; Yamagata University Hospital.

特集 臨床に役立つ貧血治療の実際

Ⅰ．総　論

小児期貧血の後期合併症とQOL
－成人期移行における問題点－

石田也寸志（いしだやすし）　聖路加国際病院小児科，聖ルカ・ライフサイエンス研究所臨床疫学センター

Key Words
childhood anemia
late effects
QOL
transition
Fanconi貧血

要旨

小児期貧血のうち，おもに遺伝性球状赤血球症・赤血球酵素欠損症・サラセミアなどの先天性溶血性貧血の後期合併症，外来通院中・長期生活管理の留意点と患者・家族への支援，成人への移行例の問題点について解説する．また，Fanconi貧血とDiamond-Blackfan貧血の後期合併症（とくに発がんと内分泌学的な問題）と妊娠出産に関する問題点について述べる．

はじめに

小児期にみられる貧血としては，鉄欠乏性貧血がもっとも多く，それ以外に溶血性貧血としては遺伝性球状赤血球症に代表される先天性のものと，Coombs抗体による自己免疫性貧血に代表される後天性のものがあり，これら以外に血液専門医の診断や治療が必要な再生不良性貧血や白血病などがある．

本特集において，乳幼児期鉄欠乏性貧血の発達・知能への影響は「鉄欠乏性貧血－食育の観点から－」の稿で論じられ，長期輸血に伴う合併症は「小児に対する輸血療法」の稿で詳述される．また，再生不良性貧血や造血幹細胞移植に関連する合併症やQOLの問題も他稿で論じられている．白血病などの小児がんにおいては，特有の後期合併症とQOLの問題がある[1]ので，本稿では，小児期貧血のうち遺伝性球状赤血球症をはじめとする先天性溶血性貧血とFanconi貧血・Diamond-Blackfan貧血などの小児期に特有の比較的まれな貧血疾患のlate effects（後期合併症）とQOL（移植症例を除く）に関して解説し，生活管理上の注意点や成人期医療への移行における問題点などについて述べる．

先天性溶血性貧血（遺伝性球状赤血球症・赤血球酵素欠損症・サラセミア・不安定Hb症）に関して[2)3)]

1．治　療[2)4)]

先天性溶血性貧血に対しては，摘脾がもっとも有効な治療法である．摘脾の適応や欧米のガイドラインについては，「先天性溶血性貧血」の稿で詳述される．摘脾後の重篤な細菌感染症（敗血症）の合併に関して，非常にまれではあるが小児期に摘脾をした後，成人になってから肺炎球菌による敗血症や髄膜炎を合併したとい

0386-9806/09/¥100/頁/JCLS

う報告[5]もみられ，成人期以降も注意が必要である．そのため最近では，部分摘出（70～80％摘出，partial）にとどめる工夫や，ごく少量脾臓を残す方法（93～99％摘出，near-total）なども検討されている．

また最近では，摘脾の後期合併症として感染症以外に心血管病（とくに血栓症や肺高血圧症）が指摘されており[6][7]，軽症例における摘脾の適応は慎重に選択する．なお，輸血を長期間必要とする例では，鉄過剰症の可能性をいつも念頭において，「小児に対する輸血療法」の稿を参考に除鉄療法を併用する．また，サラセミアや異常ヘモグロビン（以下，Hbと略す）症に対しては，造血幹細胞移植も行われる．

2. 外来通院中・長期生活管理の留意点

1）学校生活の留意点（表1）

グルコース-6-リン酸脱水素酵素（以下，G6PDと略す）異常症や不安定Hb症などでは，酸化作用を有する薬剤（とくに解熱薬，サルファ薬，抗マラリア薬）の服用により溶血発症をおこすことがある．感染症罹患そのものも誘因となるが，薬剤投与を受けていることが多く，誘因を特定できないことも少なくない．急性溶血発作の予防のためソラマメの摂取を避け，薬剤を服用する際には主治医に相談するように患者や家族に指導する[8][9]．

表1 グルコース-6-リン酸脱水素酵素異常症の溶血発作の原因（文献8）9）より引用）

1. 医薬品
プリマキン（抗マラリア薬）
スルファメトキサゾール（サルファ薬）
ナリジクス酸（キノロン系抗生物質）
ドキソルビシン（抗腫瘍薬）
2. 化学物質
ナフタレン（防虫剤）
メチレンブルー（染色剤）
トルイジンブルー（染色剤）
3. 食物
そら豆（実，花粉）
4. 病態・疾患
感染症（ウイルス，細菌）
糖尿病性アシドーシス

2）気をつけるべき感染症

遺伝性球状赤血球症を含むすべての遺伝性溶血性貧血では，骨髄で赤芽球系過形成になっているため，パルボウイルスB19感染などにより骨髄無形成発症をおこすことがある．その際，貧血は急速に出現し心不全に至ることもあり，輸血が必要となることが多い（詳しくは「先天性溶血性貧血」の稿を参照）．

3）高ビリルビン血症の持続による胆石症

10歳以下ではまれといわれているが，成人では半数以上の患者で認められる．溶血の著明な患者や体質性黄疸を合併する例では胆石症の頻度が高く，しかも小児期から認められることが多くなる[10]．急性腹症などの際に，胆石症発作を念頭において診察することが必要になることもある．

3. 患者・家族への支援

1）病名告知と遺伝カウンセリング[11]

①遺伝性球状赤血球症

多くは常染色体優性遺伝様式をとるが，中には常染色体劣性遺伝を示す例や孤発例もある．

②G6PD異常症

伴性劣性遺伝様式をとり，臨床上問題となるのはヘテロ接合の男性にほぼ限られる．

③ピルビン酸キナーゼ（PK）異常症

常染色体劣性遺伝であり，臨床上問題になる溶血を呈するのはホモ接合ないし異なる二つの異常遺伝子の複合ヘテロ接合症例の場合である．

④サラセミア

わが国のβサラセミアは軽症型であるヘテロ接合症例が大部分で，中間型（おもにホモ接合，複合ヘテロ接合）が6.4％を占める．注意すべき点は，ヘテロ接合症例の血族結婚により重症サラセミアが出現しうることである．

⑤不安定Hb症（先天性Heinz小体性貧血）

常染色体優性遺伝で，慢性溶血や薬剤惹起性溶血をきたすのはヘテロ接合である点が重要で

ある．ホモ接合は致死的と考えられる．

2）小児慢性特定疾患治療研究事業

2005年の制度改正により，軽症と認められるものは対象外となるなど，疾患名と疾患の状態により承認基準が変更されており，下記のような条件がつけられているので申請の場合には注意が必要である．

①遺伝性球状赤血球症・G6PD異常症・ピルビン酸キナーゼ（PK）異常症

検査で，血中Hb値10.0 g/dL以下，または赤血球数350万/μL以下の状態が持続する場合．

②サラセミア・不安定Hb症

治療で，継続的に補充療法もしくは除鉄剤の投与を行っている場合，または造血幹細胞移植を実施する場合．

4．成人への移行例の問題点

1）キャリーオーバー症例（結婚・出産）の抱える問題

遺伝性球状赤血球症では感染症，生理・妊娠や薬剤投与，軽症サラセミアでは感染症や妊娠，G6PD異常症では感染症や糖尿病性アシドーシスに伴い，急激な貧血の増悪や溶血発症がみられることがある[8]．また，遺伝様式により疾病罹患の危険性が異なるので，遺伝相談では遺伝様式に関する正確な情報を伝える．

2）サラセミアの神経認知力と成人移行の問題[12) 13)]（表2）

Economouら[14]は，βサラセミア32例（平均年齢14.5歳）の神経認知学的な検討を行い報告している．脳幹聴覚反応，視覚・感覚誘発反応で異常を示したのは1名のみであったのに対し，神経伝導速度は6名（18.8％）で異常を示し，総合的なIQが異常値を示したのは36.4％で，22小児例のうち8名はIQが85未満（8名中3名は70未満）であった．しかし，知能予後に影響を与える危険因子は抽出できなかったと報告している．

Musallamら[15]によると，サラセミアの生命予後の改善とともに，小児期から成人期に至る過程で種々の問題がおきているとされる．

表2[15]に示したように，成人医療施設にはサラセミアの専門家がいないうえ，小児サラセミアセンターでは成人医療の専門家や心理専門家がいない．そのため，成人期に移行したサラセミア症例の診療やケアが十分に行えない状況になっていると指摘している．ただし，この問題

表2　サラセミアにおける成人期ヘルスケア移行の問題点（文献15）より引用）

ドメイン		問題点	推　奨
臨床	診療形態 スタッフ・専門家	ハードウエア 小児サラセミアセンターに成人医療専門家や心理学者がいない 成人医療施設にサラセミア専門家がいない 成人医療移行の問題への関心の欠如	機器の変更 不足しているスタッフを雇用 資金や方針の提供
研究		成人期の医療移行に関する研究の欠如	社会心理学的な研究を増やし，コンプライアンスを改善させるような治療方式を確立する
社会心理	教育	病気の自然歴に対する認識	社会心理的なサポート
	自立	身体的	財政的・指導的サポート
		心理的	社会心理的なサポート
	就労	治療や疲労感による長期欠勤	社会心理的なサポート
	人間関係	恥ずかしさや社会の不寛容により制限される	社会心理的なサポート
	結婚	財政的，性的，感情的な重荷	社会心理的なサポート
	精神的問題	精神疾患に罹患しやすい	社会心理的なサポート