Late effects after hematopoietic stem cell transplantation in patients with HLH: A Histiocyte Society, PDWP, IEWP, and TCWP EBMT Study

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Background: Hematopoietic stem cell transplantation (HCT) is the only curative treatment in primary hemophagocytic lymphohistiocytosis (pHLH). However, HCT is associated with a wide range of late effects (LEs).

Objective: We sought to characterize the long-term outcome and LEs following HCT in pHLH.

Methods: A total of 274 children with pHLH from the European Society for Blood and Marrow Transplantation registry who underwent allogeneic HCT between 2004 and 2015 were included. Multivariable logistic regression models were used to evaluate the adjusted impact of baseline variables on central nervous system and hormonal LEs, respectively.

Results: A broad spectrum of LEs was identified, with neurologic (31%) and hormonal (34.8%) complications being the most prevalent. Chemotherapy (HLH-1994/HLH-2004) before HCT was identified as a significant risk factor for endocrinological LEs ($P = .03$), highlighting a novel aspect not previously reported. The presence of neurologic abnormality at diagnosis was an independent risk factor for neurologic LEs ($P < .001$) as was incomplete remission status at the time of HCT ($P = .04$).

Conclusions: HCT has significantly improved survival in patients with pHLH. However, survivors still face significant risks of LEs. (J Allergy Clin Immunol 2026;157:486-94.)

Key words: *Primary hemophagocytic lymphohistiocytosis, familial hemophagocytic lymphohistiocytosis, hematopoietic stem cell transplantation, late effects*

Primary hemophagocytic lymphohistiocytosis (pHLH) is a hyperinflammatory condition characterized by failure of

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Abbreviations used
CNS: Central nervous system
CR: Complete remission
CSF: Cerebrospinal fluid
EBMT: European Society for Blood and Marrow Transplantation
FHL: Familial hemophagocytic lymphohistiocytosis
GvHD: Graft-versus-host disease
HCT: Hematopoietic stem cell transplantation
HLH: Hemophagocytic lymphohistiocytosis
LE: Late effect
MAC: Myeloablative conditioning
OR: Odds ratio
OS: Overall survival
pHLH: Primary hemophagocytic lymphohistiocytosis
sHLH: Secondary hemophagocytic lymphohistiocytosis
XLP1: X-linked lymphoproliferative disease type 1

apoptosis due to absent or reduced cytolytic functions of natural killer cells and cytotoxic T lymphocytes.[1-3] The functionally defective natural killer cells and cytotoxic T lymphocytes will, in response to a normal trigger (eg, a common virus), induce an abnormal immune response, leading to hyperinflammation mediated by key cytokines such as IFN-γ, IL-1b, and IL-18. Underlying genetic causes have been identified in autosomal-recessive familial HLH 2-5 (FHL2-5), Griscelli syndrome type 2, Chediak-Higashi syndrome, X-linked lymphoproliferative disease type 1 (XLP1), and X-linked inhibitor of apoptosis deficiency.[4-6]

Currently, the only curative treatment for pHLH is hematopoietic stem cell transplantation (HCT). However, early diagnosis and efficient pre-HCT treatment of hyperinflammation are key components for the overall survival (OS). The purpose of the induction therapy is to suppress hyperinflammation and obtain remission before HCT, which is known to influence survival in patients with pHLH.[7,8] After introduction of the etoposide-based induction protocol (HLH-94), survival improved significantly, although the 5-year OS was only approximately 60%.[9-11] Lately, a better understanding of the pathophysiology of pHLH has provided new approaches with targeted immunotherapies. The anti-CD52 antibody alemtuzumab has been shown to be efficient in refractory pHLH[12] as well as in first-line treatment, with an OS of 92% before HCT.[13] Approaches targeting the hypercytokinemia in pHLH, such as Janus kinase 1/2 inhibitors[14] and biological agents such as IFN-γ–blocking antibodies,[15,16] have also shown promising results and will likely play an important role in the future.

The improvement in rapid diagnosis, induction treatment, transplant conditioning regimen, and supportive care has had a positive effect on OS in pHLH. However, in general, pretransplant treatment exposure, transplant conditioning regimen, and transplant-related complications are associated with a wide range of adverse late effects (LEs), and every organ can be affected, resulting in morbidity and late mortality. Previous studies of LEs following HCT for malignant and nonmalignant diseases have described cardiovascular, pulmonary, endocrine, and renal LEs as well as infertility, iron overload, bone disease, and neuropsychological problems.[17-20] The leading causes of late mortality include malignancy, lung disease, infections, secondary cancers, and chronic graft-versus-host disease (GvHD).[21] In patients with pHLH, there is a lack of long-term follow-up studies after HCT, and the risk of LE morbidity has been described only in small cohorts.

We present a literature review of LEs following HCT for pHLH and a retrospective, registry-based study of LEs in 274 children with pHLH following allogeneic HCT.

METHODS

Literature search methodology

A systematic literature search was undertaken at the library of Karolinska Institute, Stockholm, Sweden. MEDLINE, Embase, Web of Science, and PubMed databases were searched according to the guidelines of the Preferred Reporting Items for Systematic Review and Meta-analysis statement.[22] Participants were children (<18 years) who underwent HCT for pHLH or secondary HLH (sHLH). The primary outcome measure was LEs. The search included Medical Subject Headings terms in titles, abstracts, as well as full texts. The search terms and key words included were as follows: "infants," "children," "HLH," "FHL," "MAS" (macrophage activation syndrome), "HCT," and "possible late effects." Selected articles were published between January 1995 and July 2020.

Patients and data collection of LEs

To assess the incidence of LEs in patients with pHLH after HCT, we undertook a retrospective cross-sectional study by the Histiocyte Society and the Paediatric Diseases Working Party (PDWP), Inborn Errors Working Party (IEWP), and Transplant Complication Working Party (TCWP) of the European Society for Blood and Marrow Transplantation (EBMT). The study was approved by the scientific committees of the societies. Because FHL2-5, Griscelli syndrome type 2, Griscelli syndrome type 2, CHD, and XLP1 share a common pathophysiology involving impaired cytotoxic lymphocyte function, they were classified as pHLH. Other primary immunodeficiencies were excluded, because HLH is not a defining clinical feature and arises through distinct mechanisms. From the EBMT registry, 506 children (<18 years) diagnosed with pHLH at the center, on the basis of either genetic confirmation or family history, who underwent allogeneic HCT between 2004 and 2015 and survived 2 years or longer posttransplant were identified.

Transplantation-related data for each patient were extracted from the EBMT registry and included age, sex, details regarding HCT, type of conditioning regimen, and outcome data. A supplementary data questionnaire on selected LEs was designed by the LEs working party of the Histiocyte Society. Selected LEs were graded as per St Jude Lifetime Cohort severity grading.[23] The questionnaire was sent to 98 pediatric HCT centers within the EBMT for each eligible patient. A total of 314 (62%) questionnaires from 37 centers were returned. In case of missing or incomplete data, an EBMT data manager contacted the center and completed the data. Individual patients were not contacted. Eleven patients were excluded because of difficulties for the centers to produce information

on LEs, 15 patients were excluded for inaccurate or unclear diagnosis, and 14 patients with sHLH were excluded. Participating centers and number of patients provided by each center are provided in Table E1 (in the Online Repository available at www.jacionline.org).

Informed consent for transplantation and data collection in the EBMT registry was obtained locally according to regulations applicable at the time of transplantation. Since January 1, 2003, all centers are required to obtain written informed consent before data registration following the Helsinki Declaration 1975. Ethical permission for this study was obtained by the Swedish Ethical Reviews Authority. Data processing was carried out in accordance with the standards for patient confidentiality and good clinical practice.

Statistical analysis

To estimate the incidence of LEs, patients with at least 2 years of follow-up were selected. The median follow-up estimated using the reverse Kaplan-Meier method was 8.2 years (95% CI, 7.5-8.7). Collecting retrospectively the exact date of each LE was not possible. Death was considered a competing event of each LE, although we observed only 11 deaths. Given the completeness of follow-up, the low number of deaths, and the difficulty of retrospectively collecting an exact date of onset for LEs, the LEs were evaluated as binary outcomes rather than time-to-event outcomes.

The LEs related to central nervous system (CNS) outcomes were neurocognitive disturbance, paralytic disorder, seizures, peripheral sensory, and other neurologic dysfunction. The LEs related to hormonal outcomes were thyroid dysfunction, growth hormone deficiency, and gonadal dysfunction. The binary CNS LE and the binary hormonal LE were defined as occurrences of at least 1 of the stated LEs. Other collected LEs were cardiac dysfunction, pulmonary defects (including obstructive defects, restrictive defects, and diffusion defects), gastrointestinal disorders (not due to GvHD), chronic kidney disease, liver dysfunction, ocular dysfunction, hearing problems, dental problems and oral health, obesity, alopecia, and bone-related LEs (including osteoporosis, osteonecrosis, and other bone abnormalities).

Quantitative variables were presented as median, quartiles 1 and 3, and minimum and maximum. Qualitative variables (including LEs) were presented as number and percentage. Univariable impact of baseline variables on CNS and hormonal LEs was tested using the Wilcoxon test for quantitative baseline variables and the chi-square or the Fisher exact test for qualitative baseline variables. Multivariable logistic regression models were used to evaluate the adjusted impact of baseline variables on CNS and hormonal LEs, respectively. Baseline variables included in the multivariable logistic model for CNS LEs were the presence of clinical neurologic abnormalities before the HCT, chemotherapy used before HCT, disease status at HCT, type of HLH diagnosis, donor type, myeloablative conditioning (MAC) regimen, natural logarithm of the time from diagnosis to HCT, and natural logarithm of the age at diagnosis. Baseline variables included in the multivariable logistic model for hormonal LEs were the same as for CNS LEs except the presence of neurologic abnormalities before HCT. The impact of baseline variables is presented as odds ratio (OR) with their 95% CIs. OS was calculated using the Kaplan-Meier estimator. All tests were 2-sided with a 5% alpha rate. All analyses were completed using the statistical R software version 4.0.2 (R Foundation for Statistical Computing, Vienna, Austria).[24]

RESULTS

Literature review

In total, 1254 articles were identified. Abstracts and articles referring to patients with HLH who had undergone HCT and reported data on long-term follow-up were included. Articles containing case reports, only small series of cases, or abstracts only were excluded. Each article identified during the initial inclusion process (n = 297) was obtained in full text and, if assessed relevant, included in the systematic analysis. In total, 7 of the retrieved publications met the criteria: children diagnosed with any form of HLH, younger than 18 years at the time of HCT, and systematic assessment of LEs excluding acute toxicity. Four articles reported on patients with HLH only, and 3 articles described patients with other conditions including patients with HLH.

The incidence of LEs after HCT was highly variable, ranging from 7% to 52%.[25,26] A summary of patient characteristics in the 7 reviewed publications is provided in Table I.[25-30] The incidence of neurologic LEs in HLH after HCT varied between 7% and 26%.[9,25] The severity varied from mild neurologic disorders to severe neurologic impairments.[9,25-27] The incidence of nonneurologic LEs in HLH after HCT ranged from 18% to 58%.[25] The most frequent reported LEs not affecting CNS were short stature and other endocrinological problems. Neurologic LEs (severe mental impairments, seizures, developmental and neurocognitive delays, and attention-deficit/hyperactivity disorder) occurred somewhat more frequently in cases with pHLH (31%) than in cases with sHLH (19%) ($P = .05$).

Patient demographic characteristics pre-HCT and at HCT

The patient cohort consisted of 274 unique patients with pHLH transplanted at 37 centers. The baseline demographic characteristics of patients in terms of age, sex, diagnosis, pre-HCT, and HCT at their first transplantation are provided in Table II. As expected, children were young at diagnosis with a median age of 5 months (range, newborn to 17 years). There were 113 (41%) male and 161 (59%) female patients. The genetic defects were known in 241 patients and unknown in 33 patients, including 4 patients not investigated. The most common genetic abnormalities were FHL2 and FHL3.

Neurologic clinical symptoms at the time of pHLH diagnosis were reported in 77 of 264 (29%) patients, with the most common symptom being seizures (13.8%) followed by development delay (12.4%), motor weakness (12%), and cognitive impairment (9.6%). Data of the pathology of the cerebrospinal fluid (CSF) were missing in a large proportion of the patients. However, at time of diagnosis, CSF positive for neopterin was reported in 5 of 20 patients, elevated CSF protein in 37 of 129 patients, and elevated CSF white blood cell count in 52 of 149 patients. Hemophagocytosis in CSF was identified in 20 of 130 patients.

The median age at HCT was 1.1 years (range, 0.1-17.3) and the median time from diagnosis of pHLH to transplantation was

TABLE I. Summary of literature reviewed

Study	Study design	No. of participants (HLH/total number)	No. of survivors (HLH/total number)	Pre-HCT therapy	Median age (mo) at HCT (range)	Median follow-up of survivors (range) (y)	Conditioning regimen (MAC, RIC, NS)	Donor (MFD, MMFD, MUD, MMUD)*
Ouachée-Chardin et al[25]	Retrospective	48/48	28	DE = 15; O = 33†	6 (12-234)	5.8	MAC = 45; NS = 3	MFD = 14 (sibling = 14); MMFD = 29 (haplo = 29); MUD = 5
Cesaro et al[27]	Retrospective	61/61	39/39	DE = 50; O = 8‡; NS = 3§	16.8 (3.24-190.8)	5.5 (2.1-18)	MAC = 50; RIC = 11	MFD = 12 (sibling = 12); MMFD = 14; MUD = 35
Ohga et al[26]	Retrospective	57/57‖	41/41‖	DE = 30; O = 16¶; NS = 11	EBV-HLH: 70.8 (16.8-216); FHLH: 14.4 (4.8-180)	EBV-HLH: 5.5 (0.3-16); FHLH: 4.8 (0.2-19)	MAC = 42#; RIC = 14	MFD = 8; MMFD = 4 (haplo = 4); MUD = 24; MMUD = 17
Trottestam et al[9]	Prospective	124/124	82/82	DE = 124	Data not provided	6.5 (4.7-18.6)	MAC = 69; NS = 55	MFD = 31; MMFD (haploidentical) = 21; MUD = 46; MMUD = 18; missing = 8
Jackson et al[28]	Prospective	21/14 (sibling controls)	21/14	DE = 21	12.7 (3.6-90)	4.9	MAC = 5; RIC = 16	MFD = 2 (sibling = 1); MMFD = 5 (haplo = 3); MUD = 6; MMUD = 8
Myers et al[29]	Retrospective	56/114	56	NS = 3	61.2 (2.4-324)	4 (1.8-8)	RIC = 115*	MFD = 27; MMFD = 1; MUD = 56; MMUD = 30
Faraci, et al[30]	Retrospective	7/137	7/137	Data not provided	132.5 (60-222.6)*	7.79 (2.07-22.69)*	MAC = 7, all busulfan-based	Data not provided

DE, Dexamethasone + etoposide; *MFD*, matched family donor; *MMFD*, mismatched family donor; *MMUD*, mismatched unrelated donor; *MUD*, matched unrelated donor; *NS*, not specified; *O*, other; *RIC*, reduced-intensity conditioning.
*The data represent the entire cohort and not only patients with HLH.
†Received personalized therapy consisting of etoposide and/or prednisone and/or cyclosporine A.
‡No therapy with pHCT.
§A total of 57 patients: pHLH in 43 patients (including 1 who underwent autologous transplant) and EBV-HLH in 14 patients (including 3 who underwent autologous/syngenic transplant); 41 survivors including pHLH in 29 survivors and EBV-HLH in 12 survivors (including 2 survivors who underwent autologous or syngenic transplant).
‖Multidrug chemotherapy, CHOP-etoposide–based regimen (etoposide vincristine, cyclophosphamide, doxorubicin, and prednisolone), was chiefly used.
¶EBV-HLH: MAC in 11 and RIC in 3; pHLH: MAC in 31 and RIC in 11.
#EBV-HLH: MFD in 1, MMFD in 2, and MUD in 5; pHLH: MFD in 7, MMFD in 2, MUD in 21, and MMUD in 12; auto/identical was performed in 3 in EBV-HLH and 1 in pHLH.

5.3 months (range, 0.3-132.1). Most patients (204 of 268 [76%]) received pre-HCT induction treatment. MAC regimens were used in most of the patients (202 of 274 [74%]), with a busulphan-cyclophosphamide regimen as the most common. Most patients received transplants from matched related donors (MRDs), (97 of 274 [35%]), followed by mismatched unrelated donors (76 of 274 [28%]), matched unrelated donors (69 of 274 [25%]), and mismatched donors (32 of 274 [12%]). CNS disease was not fully controlled in about a third of the patients at the time of HCT (57 of 211 [27%]), but data on CNS disease at HCT were missing for 63 patients. Similarly, 73 of 268 patients (27%) were not in complete remission (CR) at the time of HCT.

Survival and events after HCT

The outcomes after first HCT are provided in Table III. The median follow-up time was 8.2 years (95% CI, 7.5%-8.7%). The OS at 8 years after HCT considering the population cohort defined as alive at 2 years after HCT was 96.1% (95% CI, 92.9%-97.9%). There were 11 deaths in the population cohort, and characteristics of these patients are provided in Table IV.

Acute GvHD of any grade was observed in 103 of 273 patients (38%), and of these, acute GvHD grades II to IV were observed in 64 patients (23%). Chronic GvHD was observed in 41 patients (15%). At 1 year after HCT, a full donor chimerism was seen in 156 patients (63%) and a mixed chimerism in 72 patients (29%). Sixteen patients (6.5%) experienced engraftment failure, 2 patients rejected with complete reconstitution of recipient alleles, and 1 patient rejected without reconstitution of recipient alleles. Chimerism at 1 year post-HCT by conditioning regimen is provided in Table E2 (in the Online Repository available at www.jacionline.org). Thirty-three patients (12%) needed a consecutive HCT, and the leading cause for retransplantation was rejection/graft failure. The Lansky scores at last follow-up were available for 226 alive patients. Of these, the score was normal for 173 patients (77%), and in 27 patients (12%) it was normal with minor restrictions in strenuous physical activity. In 5 patients (2%), the Lansky score was 50 or less, indicating a significant impact on normal activity and function. Seven patients (3%) developed a secondary malignancy, and of these, 2 patients were diagnosed with acute leukemia, 4 with lymphoma, and 1 with myelodysplastic syndrome (see Table E3 (in the Online Repository available at www.jacionline.org).

Late effects

Fig 1 shows the incidence and type of LEs identified. The most common LE reported was hormonal (34.8%) and the second most

TABLE II. Patient demographic characteristics and HCT conditions at first HCT

Variables	Modalities	N = 274
Age (y) at diagnosis	Median (IQR)	0.4 (0.2-2.1)
	Range	0-17
Sex	Female	113 (41.2)
	Male	161 (58.8)
Diagnosis	pHLH (genetic testing not done)	4 (1.5)
	pHLH (no abnormalities detected)	29 (10.6)
	FHL2 (*PRF1*)	49 (17.9)
	FHL3 (*UNC13D*)	61 (22.3)
	FHL4 (*STX11*)	14 (5.1)
	FHL5 (*STXBP2*)	33 (12)
	CHS (*LYST*)	16 (5.8)
	GS2 (*RAB27A*)	42 (15.3)
	XLP (*SH2D1A*)	26 (9.5)
Pre-HCT chemotherapy treatment*	No	64 (23.9)
	Yes	204 (76.1)
	Missing	6
Disease status at transplant	CR	195 (72.8)
	Non-CR	73 (27.2)
	Missing	6
Age (y) at transplant	Median (IQR)	1.1 (0.6-3.2)
	Range	0.1-17.3
Karnofsky Performance/ Lansky play-performance scale at transplant	<90	65 (40.4)
	≥90	96 (59.6)
	Missing	113
Time (mo) between diagnosis and HCT	Median (IQR)	5.3 (3.3-9.1)
	Range	(0.3-132.1)
Donor type	MRD	97 (35.4)
	MMR	32 (11.7)
	MUD	69 (25.2)
	MMUD	76 (27.7)
Female donor to male recipient	No (all other combinations)	199 (74.5)
	Yes (female donor to male recipient)	68 (25.5)
	Missing	7
Ex vivo TCD	No	227 (86.3)
	Yes	36 (13.7)
	Missing	11
In vivo TCD	No	62 (24)
	ATG	140 (54.3)
	Campath	56 (21.7)
	Missing	16
GvHD prophylaxis	CSA-based	59 (23)
	CSA + MMF	47 (18.3)
	CSA + MTX	95 (37)
	CSA + MTX + MMF	1 (0.4)
	Other	55 (21.4)
	Missing	17
Myeloablative regimen	No	72 (26.3)
	Yes	202 (73.7)
Conditioning regimen	BuCy-based	113 (41.2)
	BuFlu-based	60 (21.9)
	FluMel-based	50 (18.2)
	Treo-based	43 (15.7)
	TBI + BuCy	1 (0.4)
	Other combinations	7 (2.6)

All data are presented as n (%), unless otherwise specified.
ATG, Antithymocyte globine; *BuCy*, busulphan + cyclophosamide; *BuFlu*, busulfan + fludarabine; *Campath*, anti-CD52; *CHS*, Chediak-Higashi syndrome; *CSA*, cyclosporine A; *FluMel*, fludarabine + melphalane; *GS2*, Griscelli syndrome type 2; *IQR*, interquartile range; *MMF*, mycophemolate mofetil; *MMR*, mismatched related donor; *MMUD*, mismatched unrelated donor; *MRD*, matched related donor; *MTX*, metothrexate; *MUD*, matched unrelated donor; *TBI*, total body irradiation; *TCD*, T-cell–depleted; *Treo*, treosulfan.
*Pre-HCT chemotherapy treatment is protocol HLH-94 or protocol HLH-04.

common was neurologic (31%). Cardiovascular LEs were found in 9.5%, with hypertension as the most common symptom. Pulmonary LEs were found in 18 of 210 patients (8.6%), gastrointestinal disorders (not due to GvHD) in 29 of 270 patients (10.7%), chronic kidney disease LEs in 10 of 273 patients (3.7%), liver dysfunction in 17 of 243 patients (7%), ocular dysfunction in 42 of 269 patients (15.6%), hearing problems in 25 of 271 patients (9.2%), dental problems and oral health LEs in 32 of 268 patients (11.9%), obesity in 23 of 274 patients (8.4%), alopecia LEs in 4 of 264 patients (1.5%), and bone-related LEs in 21 of 254 patients (8.3%). Severity for each LE was graded as per St Jude Lifetime Cohort severity grading.[22]

Neurologic LEs

Neurologic LEs were reported in 85 of 274 patients (31%). The median interval between HCT and diagnosis of a neurologic LE was 3.1 years (range, 0.2-12.1 years), with data missing for 9 patients. The most common LE was neurocognitive disturbance, which was reported in 63 of 267 patients (24%). Among the 63 patients with neurocognitive disturbance, most patients had a mild form (30 of 63 [47%]); however, moderate and severe forms were nearly equally distributed in the remaining patients (15 of 63 [24%] and 11 of 63 [18%] patients, respectively). In 7 patients (11%), the mild/moderate and severe classification were not stated. Paralytic disorder was observed for 11 of 270 patients (4.1%), seizures for 22 of 271 patients (8.1%), and peripheral sensory disorder for 9 of 271 patients (3.3%). Three patients had other neurologic dysfunctions. Sixty-nine, 11, 4, and 1 patient had respectively 1, 2, 3, and 4 neurologic LEs reported.

Two factors were found significantly associated with the development of neurologic LEs after HCT (Table V). First, the risk of neurologic LE was more common in patients who had CNS involvement at any time before HCT compared with those without CNS involvement (OR, 4.68; 95% CI, 2.51-8.90; $P < .001$). CNS involvement at diagnosis was defined as presence of a clinical neurologic symptom and/or a pathological CSF at any

TABLE III. Event after HCT

Variables	Modalities	N = 274
Acute GvHD	No acute GvHD present	170 (62.3)
	Grade I	38 (13.9)
	Grade II	47 (17.2)
	Grade III	12 (4.4)
	Grade IV	5 (1.8)
	Present, grade unknown	1 (0.4)
	Missing	1
Chronic GvHD	No	228 (84.8)
	Limited	20 (7.4)
	Extensive	21 (7.8)
	Missing	5
DLI post-HCT	No	225 (90.7)
	Yes	23 (9.3)
	Missing	26
1-y chimerism	Full (donor)*	156 (63.2)
	Mixed/partial†	72 (29.1)
	Lost engraftment	16 (6.5)
	Patient reconstitution	2 (0.8)
	Aplasia	1 (0.4)
	Missing	27
Consecutive HCT	No	241 (88)
	Yes	33 (12)
Chimerism before consecutive HCT	Full (donor)	4 (16)
	Mixed/partial	5 (20)
	Lost engraftment	11 (44)
	Patient reconstitution	3 (12)
	Aplasia	2 (8)
	Missing	8 among 33
Cause of consecutive HCT	Rejections/graft failure	19 (65.5)
	Relapse	7 (24.1)
	Other	3 (10.3)
	Missing	4 among 33
Karnofsky/Lansky scale at last follow up	100: Normal, NED	173 (73)
	90: Normal activity/minor restrictions in strenuous physical activity	27 (11.4)
	80: Normal with effort/active, but tired more quickly	9 (3.8)
	70: Cares for self/greater restriction of play	7 (3)
	60: Requires occasional assistance/up and around; active play minimal	5 (2.1)
	50: Requires assistance/lying around much of the day; no active playing	4 (1.7)
	20: Very sick/sleeping often; play limited to passive activities	1 (0.4)
	0: Dead	11 (4.6)
	Missing	37

DLI, Donor lymphocyte infusion; *NED*, no evidence of disease.
*Full chimerism >95% donor.
†Partial/mixed <95% donor.

time before HCT. The second predictive factor was disease status at the time of HCT, and for patients not in CR the risk of neurologic LEs was increased (OR, 1.99; 95% CI, 1.04-3.85; P = .04). No significant relationship between the incidence of neurologic LEs and the following baseline variables was observed: conditioning intensity (OR, 1.08; 95% CI, 0.55-2.18; P = .82), use of chemotherapy before HCT (OR, 1.98; 95% CI, 0.92-4.46; P = .09), diagnosis (non-FHL vs FLH: OR, 1.59; 95% CI, 0.80-3.26; P = .19), donor type (relative vs unrelated: OR, 1.24; 95% CI, 0.69-2.24; P = .48), logarithm of time between diagnosis and HCT (OR, 1.05; 95% CI, 0.74-1.48; P = .78), and logarithm of age at diagnosis (OR, 0.96; 95% CI, 0.82-1.14; P = .67).

Endocrinological LEs

Endocrinological LEs were reported in 89 of 256 patients (34.8%). The median interval between the transplant and reported endocrinological LE was 4.5 years (range, 0.1-15 years). Onset of the endocrinological LE was missing in 4 patients. The most common LEs reported were thyroid dysfunction (in 43 of 274 patients [15.7%]) and growth hormone deficiency (in 41 of 248 patients [17%]). Gonadal dysfunction was reported in 23 of 248 patients (9.3%). Seventy-two patients had only 1 hormonal LE reported, whereas 16 patients had 2 hormonal LEs reported and only 1 patient had 3.

In multivariable analysis, chemotherapy before HCT was the sole predictor of an increased risk for an endocrinological LE (OR, 2.42; 95% CI, 1.13-5.51; P = .03) (Table VI). No significant relationship between the incidence of hormonal LEs and the following baseline variables was observed: conditioning intensity (OR, 1.59; 95% CI, 0.84-3.08; P = .16), diagnosis (non-FHL vs FHL: OR, 1.60; 95% CI, 0.84-3.15; P = .16), donor type (relative vs unrelated: OR, 0.90; 95% CI, 0.52-1.58; P = .72), logarithm of time between diagnosis and HCT (OR, 1.02; 95% CI, 0.74-1.41; P = .88), and logarithm of age at diagnosis (OR, 0.92; 95% CI, 0.79-1.07; P = .29).

DISCUSSION

HCT is an inevitable therapeutic intervention for survival in pHLH. However, a critical knowledge gap persists regarding the development of LEs in the pHLH survivors after HCT, and understanding the long-term challenges later in life has become an urgent imperative. Our study, which includes a comprehensive literature review and a retrospective cross-sectional analysis of patients with pHLH who underwent HCT, reveals a broad spectrum of LEs affecting various organs. The incidence reported in the literature review exhibited substantial variability and highlighted the relative paucity of data that are available regarding long-term pHLH survivors after HCT. In our retrospective cross-sectional study, encompassing the largest cohort to date, our aim was to characterize the outcomes and LEs of patients with pHLH from the EBMT registry who underwent HCT between 2004 and 2015 and survived for at least 2 years postallogeneic HCT. The findings revealed a broad spectrum of LEs, in a notable percentage of the patients, affecting various organs, with neurologic and hormonal complications being the most prevalent.

Endocrine complications, particularly gonadal dysfunction, are common in children undergoing HCT for nonmalignant diseases[17] but have not previously been studied in a cohort consisting exclusively of patients with pHLH. These LEs often arise because of the toxic effects of chemotherapy agents used in the conditioning regimens, which contribute to endocrine dysfunction through

TABLE IV. Characteristics of patients who died during follow-up

HLH diagnosis (gene mutation)	Age (y) at first HCT	Acute GvHD	Secondary malignancy	Second HCT	Chronic GvHD	Time to death	Causes of death
FHL (no mutation identified)	1.3	No	No	No	No	2.2 y	ADEM
FHL3 (*UNC13D*)	0.8	No	No	No	No	2.5 y	Relapse
GS2 (*RAB27A*)	0.7	No	MDS (0.7 y)	No	No	3.1 y	Secondary malignancy (MDS)
FHL (no mutation identified)	0.6	No	AML (11.5 y)	No	No	12.0 y	Secondary malignancy (AML)
FHL2 (*PRF1*)	0.4	Grade III (11 d)	No	No	Extensive (1.0 y)	2.9 y	Cerebral hemorrhages
FHL2 (*PRF1*)	0.4		No	Yes (3.1 y)	Extensive (3.7 y)	4.2 y	GvHD, pulmonary, and cardiac toxicity
FHL5 (*STXBP2*)	2.3	Grade II (56 d)	EBV-DLBCL (0.3 y)	No	Extensive (0.4 y)	5.2 y	GvHD and infection
FHL5 (*STXBP2*)	0.3	Grade III (64 d)	No	No	No	2.7 y	Multiple organ failure
FHL2 (*PRF1*)	2.6	Grade II (45 d)	No	No	Extensive (0.8 y)	3.9 y	Infection (H1N1)
FHL (genetics not done)	9.8	No	NHL (1.8 y)	No	Extensive (1.1 y)	4.8 y	Other (not specified)
FHL5 (*STXBP2*)	1.0	No	AML (1.0 y)	Yes (1.3 y)	No	2.1 y	Secondary malignancy and cardiac toxicity

ADEM, Acute disseminated encephalomyelitis; *AML*, acute myeloid leukemia; *GS2*, Griscelli syndrome type 2; *MDS*, myelodysplastic syndrome.

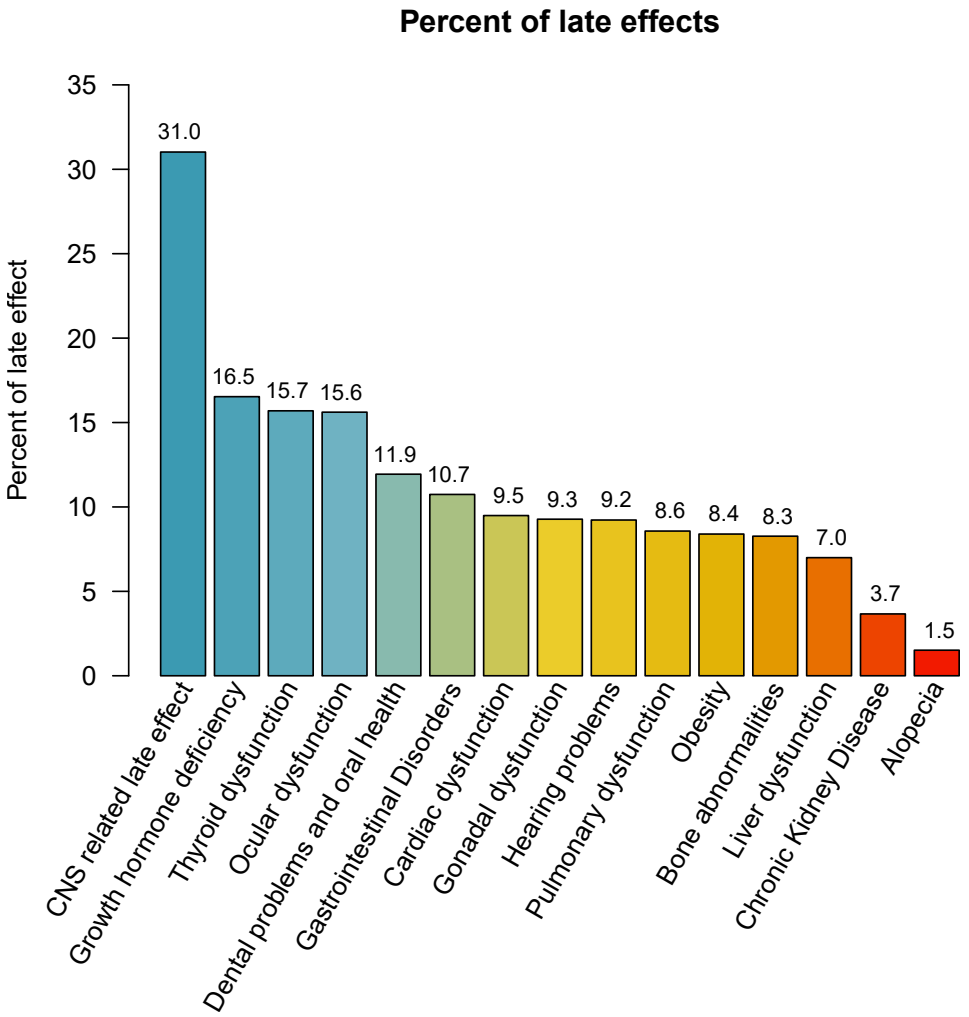

FIG 1. Distribution in percentage of LEs according to affected organ.

TABLE V. Logistic multivariable for neurologic LEs

Variables	Modalities	OR (95% CI)	*P* value
Clinical neurologic abnormality before HCT	No	1	
	Yes	4.68 (2.51-8.90)	<.001
Chemotherapy before HCT	No	1	
	Yes	1.98 (0.92-4.46)	.09
Disease status at HCT	CR	1	
	Non-CR	1.99 (1.04-3.85)	.04
Diagnosis	Other HLH	1	
	FHL	1.59 (0.80-3.26)	.19
Donor type	Relative	1	
	UD	1.24 (0.69-2.24)	.48
Myeloablative regimen	No	1	
	Yes	1.08 (0.55-2.18)	.82
log(diagnosis to HCT)		1.05 (0.74-1.48)	.78
log(age at diagnosis)		0.96 (0.82-1.14)	.67

TABLE VI. Logistic multivariable model for endocrinological LEs

Variables	Modalities	OR (95% CI)	*P* value
Chemotherapy before HCT	No	1	
	Yes	2.42 (1.13-5.51)	.03
Disease status at HCT	CR	1	
	Non-CR	0.77 (0.39-1.46)	.43
Diagnosis	Other HLH	1	
	FHL	1.60 (0.84-3.15)	.16
Donor type	Related	1	
	Unrelated	0.90 (0.52-1.58)	.72
Myeloablative regimen	No	1	
	Yes	1.59 (0.84-3.08)	.16
log(diagnosis to HCT)		1.02 (0.74-0.88)	.88
log(age at diagnosis)		0.92 (0.79-1.07)	.29

various mechanisms, including direct toxicity to hormone-producing glands, disruption of hormone signaling pathways, and damage to tissues involved in hormone metabolism and regulation. In our study, endocrinological LEs affecting the thyroid gland and growth were the most common types observed. Thyroid dysfunction is a frequently observed complication following HCT, with a similar overall reported incidence in both patients with malignant and those with nonmalignant diseases, ranging from 0% to 73%.[31] The risk of developing thyroid disease as an LE has been associated with the administration of MAC regimens.[31] However, in a study by Myers et al,[29] no difference in the risk of endocrinological LEs was observed between MAC and reduced-intensity conditioning in a cohort including 56 pHLH/XLP patients of 114 primary immunodeficiencies. Our study confirms the findings by Myers et al, showing no difference in the risk of endocrinological LEs between MAC and reduced-intensity conditioning. Notably, our analysis identified pre-HCT chemotherapy as a key risk factor, highlighting a novel aspect not previously reported. A study by van der Stoep et al[32] in children and adolescents with nonmalignant diseases showed that the effect of busulfan and treosulfan on gonadal function after HCT is not exposure-dependent. Because not all individuals in our cohort had reached puberty by the time of the last follow-up, the incidence of endocrinological LEs may be underestimated. It was also not possible to determine whether a dose-response relationship of etoposide and/or dexamethasone, used in the HLH-94 and HLH-2004 protocols, contributed to the observed hormonal LEs. Future investigations comparing patients treated within the etoposide-based HLH protocols and those who have received alemtuzumab will hopefully enhance our understanding.

Neurologic LEs are commonly observed in children following HCT of both malignant and nonmalignant diseases, stemming from diverse factors including underlying disease, conditioning regimens, immunosuppression, and complications such as GvHD.[18] In a few studies, an increased risk of developing neurologic LEs has been implicated for patients with pHLH.[9,33,34] In a study by Jackson et al,[28] the cognitive and psychosocial outcomes in a small cohort of childhood survivors with pHLH after HCT were investigated. Their results indicate that children with pHLH have significantly lower levels of intellectual functioning compared with both the population norms and the sibling controls. Factors such as age at transplantation, time to transplantation, type of conditioning, and presence of mixed chimerism were not associated with poorer cognitive outcome and, surprisingly, neither was presence of neurologic involvement at diagnosis. Whether the latter is due to neurologic involvement being underdiagnosed in pHLH could not be determined.[34] Our study indicates an elevated risk for neurologic LEs in patients with any neurologic abnormality at the time of diagnosis, but also in individuals who did not achieve CR at the time of HCT. The challenge of accurately assessing neurologic symptoms, particularly in young children, in combination with a pronounced low rate of CSF investigations in the patient cohort, suggests a risk of underdiagnosis of CNS involvement. One can speculate whether there are undetected CNS involvement in patients who failed to achieve CR, influencing their risk of developing neurologic LEs.

Although HCT remains the indispensable treatment for pHLH, our findings underscore the critical importance of accurate neurologic evaluation at the time of diagnosis and the imperative to strive for CR before HCT. However, missing data, particularly the low rate of CSF investigations, limit the interpretability of the results. Moreover, late chimerism decline is possible but is not captured in our study, potentially affecting long-term outcome. Nevertheless, given the challenges achieving CR and CNS disease control, pre-HCT development of non–chemo-based

induction therapy and alternative conditioning regimens better targeting hyperinflammation might be preferable to reduce LEs.

The risk of developing LEs also support preemptive HCT in asymptomatic siblings and, in the longer term, newborn screening as a proactive measure. Overall, our results emphasize the importance of a more tailored treatment approach, comprehensive monitoring, and management strategies to address and ultimately prevent the LEs faced by pHLH survivors after HCT.

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Clinical implications: The presence of neurologic abnormality at any time before HCT and active disease at the time of HCT seem to be independent risk factors for neurologic LEs, emphasizing the importance of careful clinical evaluation and appropriate management before HCT.

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