Cognitive and psychosocial function post hematopoietic stem cell transplantation in children with hemophagocytic lymphohistiocytosis

Jessica Jackson, BSc, DClinPsych,[a] Penny Titman, MA, MSc, PhD,[d] Stephen Butler, BA, BSc, PhD,[a] Kathryn Bond, BSc, MSc, DClinPsy,[d] Anupama Rao, MD, MRCP, MRCPath,[c] Paul Veys, FRCP, FRCPath,[b] Robert Chiesa, MD,[b] Alison Leiper, MD,[c] Lynne Riley, MRCP,[c] Kimberly Gilmour, PhD, FRCPath,[e] Persis Amrolia, PhD, FRCP, FRCPath,[b] and Kanchan Rao, MRCP, MNAMS[b] *London, United Kingdom*

Objectives: This study investigated the cognitive and psychosocial outcomes in childhood survivors of hemophagocytic lymphohistiocytosis after hematopoietic stem cell transplantation.

Methods: Twenty-one children were assessed on standardized measures of cognitive and psychosocial functioning and compared with an unaffected sibling control group (n = 14). Parent and teacher reports were obtained to provide additional information.

Results: The average full-scale intelligence quotient for the patient cohort was 81 (95% CI, 72-90), which was significantly lower than both the population average of 100 ($P = .001$) and the average for the unaffected sibling control group (99.2, $P = .002$). Fifty-six percent of school-aged children were receiving additional support at school, with the majority needing high levels of support. These children also experienced significant psychosocial difficulties. Lower socioeconomic status was associated with poorer cognitive outcomes, but age at transplantation, time to transplantation, type of conditioning, and presence of mixed chimerism were not. Ten (48%) of 21 children had evidence of neurologic involvement at diagnosis, but surprisingly, this was not significantly associated with adverse neurologic outcomes, and some children who did not have any apparent neurologic involvement at diagnosis had severe learning difficulties at follow-up.

Conclusions: In summary, childhood survivors of hemophagocytic lymphohistiocytosis are at risk of long-term cognitive and psychosocial difficulties. Prospective and systematic long-term follow-up of these patients is essential for early identification and effective management of these problems. (J Allergy Clin Immunol 2013;132:889-95.)

Key words: *Hemophagocytic lymphohistiocytosis, hematopoietic stem cell transplantation, cognitive, children, psychosocial*

Abbreviations used

CHS: Chediak-Higashi syndrome
CNS: Central nervous system
CSF: Cerebrospinal fluid
FSIQ: Full-scale intelligence quotient
HLH: Hemophagocytic lymphohistiocytosis
HSCT: Hematopoietic stem cell transplantation
IQ: Intelligence quotient
MRI: Magnetic resonance imaging
SCQ: Social Communication Questionnaire
SDQ: Strengths and Difficulties Questionnaire
SES: Socioeconomic status
UK: United Kingdom

Hemophagocytic lymphohistiocytosis (HLH) is a rare and serious disorder of the immune system that predominately affects infants and young children. The disease, which is characterized by hypercytokinemia, can be classified into primary and secondary forms, which can be difficult to distinguish clinically. Primary HLH includes familial HLH types 1 to 5, Griscelli syndrome type 2, Chediak-Higashi syndrome (CHS), X-linked lymphoproliferative disease types 1 and 2, and Hermansky-Pudlak syndrome type 2. Secondary forms of HLH are mainly associated with infections, malignancies, and rheumatologic disorders.[1,2] Neurologic involvement, which is thought to be more common in patients with primary HLH, can occur in 30% to 60% of patients at diagnosis or at recurrence of HLH.[3-5] Prompt treatment with chemotherapy and successful hematopoietic stem cell transplantation (HSCT) is the only cure for primary HLH. After a successful HSCT, neurologic manifestations can be reversed, and recurrences can be prevented.[4] However, it is now well recognized that a significant proportion of children (10% to 39%) with central nervous system (CNS) HLH have neurologic late effects ranging from mild to severe, despite successful HSCT.[4,6-8] In one of the largest studies, Horne et al[3] reported neurologic sequelae in 16 (15%) of 107 survivors treated on the HLH-94 protocol at a median follow-up of 5.3 years. Sequelae were more common in those patients with combined abnormal cerebrospinal fluid (CSF) and neurologic symptoms at diagnosis. The most common sequelae were developmental delay, epilepsy, attention deficit hyperactivity disorder, hearing loss, and hemiplegia. However, this and other studies did not analyze cognitive functioning by using standardized psychometric measures. It was our perception that in addition to what has been reported

From [a]the Research Department of Clinical, Educational and Health Psychology, University College London, and the Departments of [b]Blood and Marrow Transplantation, [c]Haematology, [d]Psychosocial Services, and [e]Immunology, Great Ormond Street Hospital for Children NHS Foundation Trust.

Disclosure of potential conflict of interest: The authors declare that they have no relevant conflicts of interest.

Received for publication February 12, 2013; revised April 12, 2013; accepted for publication May 23, 2013.

Available online August 26, 2013.

Corresponding author: Kanchan Rao, MRCP, MNAMS, Department of Blood and Marrow Transplantation, Great Ormond Street Hospital for Children NHS Foundation Trust, Great Ormond Street, London WC1N 3JH, United Kingdom. E-mail: kanchan.rao@gosh.nhs.uk.

0091-6749/$36.00

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http://dx.doi.org/10.1016/j.jaci.2013.05.046

in the literature, a larger number of children with HLH have cognitive and psychosocial impairment that is most evident at school age. In our study, for the first time, we present a detailed assessment of cognitive and psychosocial outcomes after HSCT for HLH. We compared patient outcomes with those of a control sibling group, and our results are based on multiple informants, including teacher and parental reports.

METHODS

Patients

All children given a diagnosis of primary or secondary HLH treated with HSCT between 1998 and 2009 at a single center (Great Ormond Street Hospital, London, United Kingdom) were contacted to take part in the study. Eligible participants had to be at least 1 year after HSCT and had to be at least 3.5 years old at the time of assessment because of the age constraints of the cognitive assessment. Other exclusion criteria were the presence of coexisting conditions that would have affected the patient's cognitive ability, physical ability, or both to complete the assessments, such as Down syndrome.

Fifty-three children received an HSCT for HLH in the study period, and 35 (66%) were alive at the last follow-up. Of these, 28 were older than 3.5 years and at least 1 year after HSCT. Of the 28 potential participants, 21 (75%) completed the assessment protocol, and the remaining 7 were not included for the following reasons: 1 was older then 18 years, 1 had Down syndrome, 3 declined to take part, and 2 could not be contacted. Indications for HSCT in the 21 children were as follows: primary HLH with a genetic diagnosis (n = 17), primary HLH with no genetic diagnosis (n = 2), and secondary HLH (n = 2). Before HSCT, patients received treatment according to the HLH-94 protocol up to the year 2004 and according to the HLH-2004 protocol from 2004 onward. Median time from diagnosis to transplantation was 6.7 months (range, 2.9-22 months), and median age at transplantation was 12.7 months (range, 3.6 months to 7 years and 6 months). Donors were matched sibling donors (n = 1), matched unrelated donors (n = 6), matched family donors (n = 1), mismatched family donors (n = 2), mismatched unrelated donors (n = 8), and haploidentical (n = 3). Conditioning was myeloablative in 5 patients and reduced intensity in 16 patients. Eight patients had at least 1 episode of admission to the intensive care unit during their treatment. At a median follow-up of 4 years and 11 months, 15 patients had complete donor chimerism, and 6 had mixed chimerism, ranging from 5% to 85%. All surviving patients were free of disease at last follow-up.

Neurologic involvement at diagnosis was determined from case note analysis and retrospective analysis of magnetic resonance imaging (MRI) data. Patients were categorized into 2 groups: those with and those without CNS involvement. Patients with CNS involvement had 1 or more of either clinical signs of neurologic involvement (including seizures, abnormal posturing, irritability, meningism, and cranial nerve palsies), abnormal CSF analysis, or an abnormal MRI scan result. Ten children were classified as having CNS involvement and 9 as not having CNS involvement. The neurologic status at diagnosis in 2 patients has been classified as "indeterminate" because they did not undergo CSF analysis or an MRI brain scan at diagnosis. Patient and sibling control group characteristics are detailed in Table I.

The research was approved by the London Research Ethics Committee. Informed consent was obtained according to the Declaration of Helsinki from parents and children younger than 16 years and from patients older than 16 years. Verbal assent was obtained in younger children between the ages of 8 and 15 years.

Unaffected sibling control group

The patient group differed from the United Kingdom (UK) population in terms of socioeconomic background, the high number of families from ethnic minority backgrounds, and the high number of families in which English was not their first language. A group of unaffected siblings was recruited to match for social and ethnic background to control for these factors. Siblings were assessed on the same measures of cognitive functioning, and parents completed questionnaire measures assessing psychosocial functioning. Of the 21 families opting into the study, 14 (66%) had an unaffected sibling aged between 3.5 and 16 years, all of whom agreed to take part in the study. In situations in which there was more than 1 sibling in the family, the child of the same sex who was closest to the patient's age was chosen.

Procedure

Assessments were completed either at the patient's home or during a follow-up clinic visit to the hospital.

Measures

Participants completed a full psychological assessment that included a cognitive assessment and standardized questionnaires assessing social, adaptive, emotional, and behavioral functioning. Information regarding families' ethnicity and first language was obtained. In addition, parents' educational and occupational histories were obtained to calculate socioeconomic status (SES) rated on a 5-point scale based on the occupation of the main earner.[9]

Cognitive function was assessed by using the appropriate Wechsler Intelligence Scale for the child's age: the Wechsler Pre-School and Primary Scale of Intelligence Third United Kingdom Edition[10] and the Wechsler Abbreviated Scale of Intelligence.[11] These produce a full-scale intelligence quotient (FSIQ) score based on subtests assessing different components of intelligence, such as verbal reasoning, general knowledge, visuospatial, and perceptual skills. The FSIQ score can be broken down into 2 components: verbal intelligence quotient (IQ) and performance (nonverbal) IQ. It was not possible to assess 1 child with profound developmental delay and autistic spectrum disorder because the child's level of ability fell below the lowest level of the Wechsler scales; however, standardized measures of the child's social, adaptive, emotional, and behavioral functioning were obtained by means of parental report.

Emotional and behavioral difficulties were assessed by using 4 standardized questionnaires. The Strengths and Difficulties Questionnaire (SDQ) is a standardized and brief screening questionnaire used to identify emotional and behavioral difficulties in children 4 to 16 years of age. It consists of 25 items covering common problem areas, including behavioral, emotional, hyperactivity inattention, and peer relationship difficulties, and 1 scale measuring prosocial behavior.[12] The 4 scales measuring problem areas were used in this study. Normative data are available based on a representative population sample of 10,000 children.[13]

The Social Communications Questionnaire (SCQ) is a brief (40-item) screening measure commonly used by clinicians to screen for suspected autism or autistic spectrum disorders. The measure allows an SCQ total score to be calculated, with a total score of 15 or greater indicative of significant social communication problems requiring further assessment.[14] For the purposes of this study, the SCQ was used as a brief screening measure to identify social communication difficulties and was not used diagnostically.

The Vineland Adaptive Behaviour Scales assess adaptive function across 4 domains, including communication, daily living skills, socialization, and motor skills.[15] The Vineland is one of the most widely used clinical tools for determining adaptive functioning, with normative data based on a representative sample of more than 3000 subjects standardized by age and with a mean score of 100 and an SD of 15.

The Pediatric Quality of Life Inventory (PedsQL) is a 23-item questionnaire measuring the health-related quality of life of children and adolescents.[16] The inventory comprises 4 core scales: physical functioning, emotional functioning, social functioning, and school functioning. These can be combined into 2 main subscales: physical and psychosocial (which includes emotional, school, and social functioning). Parental reports are age specific (5-7, 8-12, and 13-18 years), and normative data have been collected for healthy children and a number of different clinical groups.

Parents completed the same battery of questionnaires for both the patient and any unaffected sibling with the exception of 1 measure, the Vineland Adaptive Behaviour Scales, which was excluded from the sibling assessment protocol because of the lengthy completion time. The child (patient and sibling) completed 2 self-report standardized questionnaires, depending on their age; the SDQ if 11 years or older and the PedsQL if 8 years or older. In addition, teacher reports were collected for the patient group to provide

TABLE I. Characteristics of the patient and sibling control groups

Characteristic	Patient group (n = 21), no. (%)	Sibling group (n = 14), no. (%)
Sex		
Male	10 (48)	10 (71)
Female	11 (52)	4 (29)
Genetic diagnosis		
Primary HLH (n = 19)		
Perforin deficiency	11 (58)	
Griscelli syndrome	3 (16)	
CHS	1 (5.2)	
XLP like	1 (5.2)	
STXBP2	1 (5.2)	
Syntaxin 11	1 (5.2)	
No known mutation	1 (5.2)	
Secondary HLH (n = 2)		
Combined immunodeficiency with HLH	1 (50)	
Not done	1 (50)	
Donor		
Matched family donor	2 (10)	
Mismatched family donor (MMFD)	5 (24)	
Matched unrelated donor (MUD)	6 (28)	
Mismatched unrelated donor (MMUD)	8 (38)	
Conditioning		
Myeloablative	5 (24)	
Reduced intensity	16 (76)	
GVHD ≥ grade 2		
Yes	4 (19)	
No	16 (76)	
Not known	1 (5)	
Ethnic background		
White British	6 (29)	
Black African	4 (19)	
Maltese	3 (14)	
Arabic	2 (9)	
Asian	2 (9)	
White other	1 (5)	
Afro-Caribbean	1 (5)	
Black other	1 (5)	
Mixed	1 (5)	
SES category		
I. Professional	2 (9)	
II. Degree level	4 (19)	
III. Skilled manual and skilled nonmanual	4 (19)	
IV. Unskilled	5 (24)	
V. Unemployed	6 (29)	
Age*		
Age at assessment (y)	7.5 (3.3)	9.8 (2.9)
Age at transplantation (y)	2.1 (2.1)	
Age at diagnosis (y)	1.4 (2.0)	

GVHD, Graft-versus-host disease; *STXBP2*, syntaxin binding protein 2; *XLP*, X-linked lymphoproliferative disease.
*Age values are means (SDs).

information about whether the child received any additional help at school under the Special Educational Needs code of practice. The teacher version of the SDQ was also administered for the patient group for all children of school age to provide an additional perspective on the child's psychosocial functioning.

Statistical analysis

Cognitive and psychosocial functioning were analyzed by using a series of 1-sample *t* tests. Group comparisons were then made by using related, paired-sample *t* tests (or nonparametric statistical methods when the data were not normally distributed). A related-samples *t* test was chosen as opposed to an independent-samples *t* test because of the high degree of shared variance between siblings, and thus they were not treated as wholly independent samples. Correlational analyses were then carried out to examine the degree of association between measures of psychosocial function and participants' IQ scores. Univariate associations between potential sociodemographic covariates (eg, SES and age at assessment) and several medical variables (eg, age at transplantation and time since transplantation) and cognitive functioning were examined. Lastly, a series of independent-samples *t* tests were used to examine several demographic and medical variables on cognitive functioning. The statistical analyses were performed with SPSS version 16 software (SPSS, Chicago, Ill).

RESULTS

As shown in Table I, a high proportion of children came from minority ethnic backgrounds compared with the general population in the UK; 19% (n = 4) of the patient group did not speak English as their first language at home. Overall, the patient and sibling control groups were well matched in terms of their social and demographic factors; however, there were more boys in the control group and they were slightly older, although neither of these factors was associated with outcome. In the following sections the key findings will be summarized, presenting the cognitive and psychosocial outcome measures for both the HLH group and the sibling control group.

Cognitive function

Table II shows the cognitive and psychosocial outcomes for the patient and sibling comparison groups. The mean IQ score in the general population is 100 (SD, 15), and any score of less than 70 indicates learning difficulties (approximately 2% of the population). The comparisons between the patient group and the normative data and between the sibling group and the normative data are shown in Table E1 in this article's Online Repository at www.jacionline.org.

The mean FSIQ score for the patient group (n = 20) was 81 (95% CI, 72-90), which was significantly lower than the population average of 100 ($P < .001$). For the 14 patient-sibling pairs, the average IQ score for the patient group was also significantly lower than that for the sibling group (78.8 vs 99.2, $P < .005$, Table II). Mean verbal and performance IQ scores for the patient group were also significantly lower than those for the sibling group and the population normative data (Table II and see Table E1). IQ scores for 35% (n = 7) of the patients fell within the learning difficulty range of intellectual ability (<70) compared with the estimated 2% in the general population.[17]

There were no significant differences between the sibling control group and the normative data on all domains of intellectual functioning (see Table E1).

Psychosocial functioning

SDQ: Parental reports. Mean scores for the HLH group were significantly higher (indicating greater difficulties) compared with those for the sibling control group on 3 domains: total overall stress, emotional difficulties, and parental rating of the effect of these difficulties on the child and family (Table II).

When compared with normative values for healthy children, scores for the HLH group were significantly higher (indicating

TABLE II. Cognitive and psychosocial functioning of the HLH patient group compared with the sibling control group (n = 14)

Variable	HLH group		Siblings		t(df)	*P* value
	Mean	SD	Mean	SD		
Age at assessment	8.2	3.3	9.8	2.9	−1.4 (13)	.192
IQ						
Verbal IQ	82.9	18.6	99.8	17.2	−3.1 (13)	.009†
Performance IQ	80.5	19.4	100.4	12.9	−4.8 (13)	.001‡
FSIQ	78.8	20.2	99.2	15.4	−3.9 (13)	.002†
SDQ						
Total	14.4	7.9	9.3	6.8	2.1 (13)	.054*
Emotional	4.1	2.8	2.1	1.7	2.3 (13)	.040*
Conduct	2.8	2.0	2.2	2.1	0.9 (13)	.397
Hyperactivity	4.8	3.6	3.2	2.9	1.4 (13)	.190
Peer relationships	2.6	2.6	1.7	1.6	1.1 (13)	.293
Impact	2.4	3.2	0.3	0.8	2.3 (13)	.039*
SCQ	5.5	5.0	2.8	3.6	2.3 (13)	.041*
PedsQL						
Physical	70.5	20.1	90.3	19.0	−2.8 (8)	.023*
Psychosocial	56.4	14.4	80.8	17.8	−3.9 (8)	.005†
Total	61.4	12.6	84.3	16.8	−5.3 (8)	.001‡

t(df), Student *t*(distribution function).
*$P < .05$.
†$P < .01$.
‡$P < .00$.

higher rates of psychological difficulties) across all but 1 domain (total, emotional, hyperactivity, peer, and impact of any difficulties on the child), with the exception of conduct (behavioral problems, see Table E1).

There were no significant differences between the mean scores for siblings and the normative scores across all domains (see Table E1).

SCQ. The mean SCQ score was significantly higher (indicating greater social communication difficulties) for the patient group when compared with that for the sibling control group. Two children with HLH scored above the clinical cutoff, indicating clinically significant levels of social communication difficulties and warranting further investigation. No children in the sibling control group scored above the clinical cutoff.

PedsQL: Parental reports. The HLH patient group scored significantly lower than the sibling control group on both the physical and psychosocial scales of the PedsQL, indicating significantly lower quality of life compared with their siblings (Table II).

The PedsQL data were also compared against the age-matched, healthy UK normative data (see Table E2 in this article's Online Repository at www.jacionline.org) and compared with mean scores for a group of children in remission from cancer (UK cancer group, see Table E2). Both sets of normative data (healthy children and childhood cancer survivors) were taken from the PedsQL-UK standardization study carried out by Upton et al.[18] The cancer group included 61 survivors of pediatric cancer, all in long-term remission, attending an outpatient hospital clinic. This group was chosen to serve as an additional comparison group, allowing us to examine any potential differences between childhood survivors of cancer and survivors of HLH, both of whom have survived a chronic life-threatening illness.

Mean scores for the HLH group were significantly lower across all domains of the PedsQL compared with the normative data for healthy children. In addition, the mean scores for HLH group were significantly lower for the psychosocial but not the physical scale compared with the mean scores of the cancer group. This suggests that the HLH group's health-related quality of life, as rated by their parents, is somewhat lower than that of a group of cancer survivors but that these difficulties are psychosocial rather than physical.

Mean scores for the sibling groups were comparable with the scores for healthy children across all subdomains, suggesting that their health-related quality of life, as rated by the parents, is good (see Table E2).

Adaptive functioning

A measure of adaptive functioning (Vineland Adaptive Behaviour Scales parent/caregiver rating form) was completed for each of the children in the HLH group. Sibling data were not collected because of the lengthy administration time of the questionnaire. When compared with those of the age-matched normative group, the overall means for the patient group were significantly lower across all 3 domains: communication ($P < .001$), daily living ($P < .001$), and socialization ($P < .001$). Of note, patients' standard scores across all 3 domains fell within the moderately low range when compared with the normative data, suggesting an overall significant impairment in adaptive function.

Educational provision received

Eighteen children in the HLH group were of school age, 3 children were attending preschool, and all of the siblings were in full-time education. Of the 18 children with HLH attending school, 10 (56%) were receiving some additional support in school, and 9 of these 10 children needed high levels of support. Two children were in special needs schools for children with learning difficulties, 2 had statements of special educational needs (given to children with learning difficulties who require very high levels of special needs support), and 2 were in pupil referral units (schools for children with severe behavioral difficulties). As shown in Table III, only 44% were attending mainstream schools with no support compared with more than 90% in the sibling control group.

Teacher reports on the SDQ

Teacher ratings on the teacher version of the SDQ were obtained for the HLH group to provide an additional perspective on the child's psychosocial functioning at school (see Table E3 in this article's Online Repository at www.jacionline.org). The teacher ratings on the SDQ for the HLH group were significantly higher on 4 domains (total, emotional difficulties, peer relationships, and impact), indicating higher rates of psychosocial difficulties compared with the means for the UK normative data.

Factors associated with cognitive outcome

Table IV shows the FSIQ scores for the main factors associated with outcome. In contrast to some previous studies, age at transplantation was not associated with IQ scores,[19] and there was no significant correlation between FSIQ scores and time since transplantation or time between diagnosis and transplantation. In addition, there was no effect of sex and no significant differences

TABLE III. Summary of educational, cognitive, and psychosocial outcomes in the HLH group

UPN	Genetic diagnosis	Neurologic abnormalities at diagnosis	CSF analysis at diagnosis	MRI at diagnosis	IQ (range)	Educational provision	Significant psychological difficulties
1	CHS	No	Pleocytosis	Normal	58 (mild LD)	Statement of SEN	None
2	Perforin deficiency	No	Normal	Not done	58 (mild LD)	Statement of SEN	None
3	STXBP2	No	Normal	Not done	118 (average)	Preschool	None
4	Perforin deficiency	No	Normal	Not done	96 (average)	Mainstream	None
5	Perforin deficiency	No	Not done	Not done	58 (mild LD)	Pupil Referral Unit	ADHD
6	Perforin deficiency	Arching/ irritable	Normal	Normal	96 (average)	Preschool	None
7	Not done	No	Not done	Normal	82 (average)	SEN support in mainstream	Emotional difficulties
8	Perforin deficiency	No	Normal	Normal	<40 (severe LD)	Special school	Autism
9	XLP-like	No	Not done (unwell PICU)	Abnormal	122 (above average)	Mainstream	None
10	Perforin deficiency	No	Not done unwell	Not done	77 (borderline LD)	Pupil referral unit	ADHD and ASD
11	None	No	Not done unwell	Normal	70 (borderline LD)	SEN support in mainstream	Emotional and behavioral difficulties
12	Perforin deficiency	Seizure	Not done	Normal	56 (mild LD)	Mainstream	None
13	Griscelli syndrome	No	Normal	Normal	87 (average)	Mainstream	None
14	Perforin deficiency	No	Normal	Not done	60 (mild LD)	Undergoing assessment	Hyperactive
15	None	No	Pleocytosis and high protein	Normal	104 (average)	Preschool	None
16	Perforin deficiency	No	Pleocytosis	Normal	85 (average)	Undergoing assessment	None
17	Perforin deficiency	No	High protein	Abnormal	62 (mild LD)	Special school	Emotional and behavioral difficulties
18	Perforin deficiency	No	Pleocytosis	Not done	77 (borderline LD)	Undergoing assessment	None
19	STX 11	No	Pleocytosis	Abnormal	79 (borderline LD)	Mainstream	None
20	Griscelli syndrome	No	Normal	Abnormal	96 (average)	Mainstream	None
21	Griscelli syndrome	No	Normal	Normal	81 (average)	Mainstream	None

ADHD, Attention deficit hyperactivity disorder; *ASD*, autistic spectrum disorder; *LD*, learning difficulty; *PICU*, pediatric intensive care unit; *SEN*, Special Educational Needs; *STXBP2*, syntaxin binding protein 2; *UPN*, unique patient number; *XLP*, X-linked lymphoproliferative disease.

in FSIQ scores for children admitted to a pediatric intensive care unit during their transplantation compared with those not admitted. As might be expected, FSIQ scores were significantly related to SES, with a lower SES score (indicating a higher SES) associated with a higher FSIQ score. It was not possible to explore the effects of HLH type (primary vs secondary) or genetic diagnosis on cognitive outcome because of the small numbers in each group. Although the IQ scores for children receiving reduced-intensity conditioning were higher than the scores of those who received myeloablative conditioning, this difference was not significant. There was no difference between children with full chimerism and those with mixed chimerism.

Effect of neurologic involvement at diagnosis

Data on the patients' neurologic status at diagnosis are presented in Table V. Ten (48%) of 21 patients had CNS involvement at diagnosis, which was defined as having abnormal neurologic signs, an abnormal CSF analysis, or an abnormal MRI scan result.

Six patients did not have CSF analysis because they were clinically unstable at the time of presentation, and MRI scans at diagnosis were unavailable in 7 patients because they were referred from other centers and had received initial therapy before transfer to our institution. Two patients had neither CSF analysis nor MRI scans at diagnosis, and they have been classified as CNS status "indeterminate." None of the children in this study had clinically evident progressive or new neurologic disease at any time after onset of therapy.

Table V displays the mean IQ scores (verbal, performance, and FSIQ) for children presenting with evidence of neurologic involvement at diagnosis compared with those without neurologic involvement. There is no significant difference in IQ scores between these 2 groups.

DISCUSSION

To our knowledge, this represents the first study to have systematically evaluated the cognitive and psychosocial outcomes of HLH survivors. The findings of this study indicate that children treated for HLH with HSCT have significantly lower levels of intellectual functioning compared with both population norms and sibling controls. This finding was consistent across all domains of intellectual functioning (verbal IQ, performance IQ, and FSIQ), with more than 50% of children requiring significant levels of additional support at school. In line with these findings, these children also had significantly lower than average levels of adaptive functioning consistent with the level of cognitive ability observed. Although, as in previous studies,[20] we found that children from poorer SES conditions had a worse cognitive outcome, SES or environmental factors alone cannot explain the poor cognitive function of the HLH group because the

TABLE IV. FSIQ score by main predictive factors (HLH group only, n = 20)

Factor	No.	FSIQ, mean (SD)	t(df)	*P* value
PICU				
No admission	12	80.6 (17.8)	0.1 (18)	.89
Admitted	8	81.9 (23.9)		
Sex				
Male	10	78.3 (21.6)	−0.6 (18)	.54
Female	10	83.9 (18.7)		
Conditioning			Mann-Whitney *U* test	.17
Myeloablative	5	70.2 (16.4)		
Reduced intensity	15	84.7 (20.0)		
Chimerism				
Full	13	80.9 (20.0)		.94
Mixed	7	81.4 (21.1)		

Continuous variables	Correlation	*P* value
Age at transplantation	$r = 0.1$	.67
Age at assessment	$r = -0.2$	.52
Time since transplantation	$r = -0.3$	.28
Time from diagnosis to transplantation	$r = 0.18$	.44
SES (1-5)	$r = -0.5$	.04*

Note: Number of subjects was 20 because it was not possible to formally assess 1 child with profound developmental delay because her level of ability fell below the lowest level of the Wechsler scale.
PICU, Pediatric intensive care unit; *t(df)*, Student *t*(distribution function).
*$P < .05$.

TABLE V. Mean IQ scores for patients with neurologic involvement at diagnosis compared with those without neurologic involvement

	Evidence of neurologic involvement at diagnosis		
IQ scale	None (n = 8)	Abnormal MRI or CSF analysis or abnormal neurology (n = 10)	Indeterminate (n = 2)
Full scale	81.5	83.5	67.5
Verbal	86.0	88.8	71.5
Performance	82.0	83.0	72.0

Note: Number of subjects was 20 because it was not possible to formally assess 1 child with profound developmental delay because her level of ability fell below the lowest level of the Wechsler scale.

members of sibling control group were functioning in the normal range for cognitive ability. However, this emphasizes the point that all such outcome studies should use a sibling control group, where feasible, and look at SES as a significant variable.

In addition to cognitive difficulties, we also found significant psychosocial (especially emotional and social) difficulties in this group of children. These psychosocial difficulties were observed by parents and teachers, suggesting that these children are experiencing difficulties that occur across contexts. These difficulties were significant when compared with the sibling group, and parent-reported quality of life was also lower for the HLH group when compared with that of cancer survivors, suggesting that prolonged illness and hospitalization are probably not solely responsible for these challenges.

The percentage of children with significant neuropsychological problems is higher in our study than previously reported. Previous studies have reported neurologic sequelae in 15% to 39% of patients, and this is most evident in children with neurologic involvement at diagnosis.[3,6] In our study there was no significant difference in IQ scores between children who presented with CNS involvement at diagnosis compared with those who had no CNS involvement at diagnosis. However, it is possible that the actual number of children with neurologic involvement at diagnosis is underrepresented in the current study because not all children had CSF analysis and MRI scans. Conversely, 3 of 8 children with no neurologic involvement at diagnosis had significant learning difficulties (IQ score, 50-70) in our study, bringing into question the extent to which current investigations are able to detect subtle neurologic involvement in children presenting with HLH. On the basis of our findings of significant cognitive impairments in more than half of our patients, we could speculate that the incidence of CNS involvement at diagnosis is probably higher than currently recognized. Another unanswered question is the timing of the "first CNS hit" in HLH. This might happen very early in the disease process, a theory supported by the findings of Deiva et al,[8] who noted that 21% of their HLH study population aged less than 1 year had microcephaly at presentation, suggesting very early brain damage. These findings add to the ongoing controversy regarding the timing and appropriateness of HSCT in asymptomatic siblings with genetically proved HLH. There was 1 child with CHS in our study. Progressive neurologic dysfunction and low cognitive ability in patients with CHS despite successful HSCT has previously been reported.[21]

This study extends previous work in a couple of important ways. It is the first late-effects study in HLH to use a sibling control group, matching for a number of key sociodemographic factors, including SES and ethnicity. Second, a major strength of the current study is the use of more than 1 informant (parental and teacher reports) to investigate the cognitive and psychosocial outcomes and to provide an overall picture of the quality of life in these children. As with most retrospective studies, one of the limitations of this study is the use of a cross-sectional design, which precludes the examination of cognitive and psychosocial outcomes over time and prevents causal inferences. It is very difficult to obtain accurate estimates of cognitive function before transplantation in this group of children, especially when children are acutely unwell and very young at the time of diagnosis. This means that it was not possible to determine whether the observed IQ scores represent premorbid levels of intellectual functioning because of nonhematopoietic manifestations of the HLH-causative genes or whether there has been a decrease in intellectual functioning as a result of the HLH disease process, therapy, and subsequent HSCT procedure. Another limitation was the sample size. HLH is an extremely rare disease, and despite the excellent participation rates (75%), the sample size obtained was nevertheless small for detailed multivariate statistical analysis.

Larger patient numbers are needed to provide answers to difficult questions and to analyze risk factors for adverse neurologic outcomes, including the role of various gene mutations. Most patients with HLH already receive comprehensive clinical neurologic examination, CSF analysis, and neuroradiology at diagnosis. In addition, we would recommend that there should be age-appropriate cognitive assessment before HSCT and at regular intervals after HSCT and that cognitive follow-up is built into future HLH trials. Results of larger studies would have important implications for counseling of families, and early identification of cognitive and psychosocial difficulties would help to ensure that children and families receive appropriate levels

of educational support to optimize the child's learning experience.

We thank all of the children, families, and teachers who participated in the current research study.

Key messages

- **Children with HLH have a high incidence of long-term significant cognitive and psychosocial impairments, even after a successful HSCT.**
- **These impairments can occur despite no obvious neurologic involvement with the disease process at diagnosis.**

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TABLE E1. Cognitive and psychosocial functioning of the HLH patient and sibling control groups compared with normative data

	Normative data	HLH	Comparison with normative data		Sibling	Comparison with normative data
Measure	**Mean (SD)**	**Mean (SD)**	**t(df)**	***P* value**	**Mean (SD)**	**t(df), *P* value**
IQ						
Verbal IQ	100 (15)	86.0 (18.6)	−3.4 (19)	.003†	99.8 (17.2)	−0.05 (13), ns
Performance IQ	100 (15)	81.5 (19.1)	−4.3 (19)	.001‡	100.4 (12.9)	0.1 (13), ns
FSIQ	100 (15)	81.1 (19.8)	−4.3 (19)	.001‡	99.2 (15.4)	−0.2 (13), ns
SDQ						
Total	8.4 (5.8)	14.3 (7.5)	3.4 (17)	.004†	9.3 (6.8)	0.5 (13), ns
Emotional	1.9 (2.0)	3.7 (2.6)	3.0 (17)	.008†	2.1 (1.7)	0.5 (13), ns
Conduct	1.6 (1.7)	2.5 (1.9)	2.0 (17)	.063	2.2 (2.1)	1.1 (13), ns
Hyperactivity	3.5 (2.6)	5.3 (3.6)	2.1 (17)	.047*	3.2 (2.9)	−0.4 (13), ns
Peer relationships	1.5 (1.7)	2.8 (2.4)	2.2 (17)	.040*	1.7 (1.6)	0.5 (13), ns
Impact	0.4 (1.1)	2.6 (3.3)	2.9 (17)	.010†	0.2 (0.4)	−1.6 (13), ns
PedsQL						
Physical	89.1 (12.3)	68.3 (18.1)	−4.3 (13)	.001‡	88.4 (18.6)	−0.1 (10), ns
Psychosocial	81.5 (16.1)	58.7 (15.7)	−5.6 (13)	.001‡	80.3 (16.4)	−0.4 (10), ns
Total	84.6 (11.2)	62.1 (13.7)	−6.2 (13)	.001‡	83.3 (16.0)	−0.3 (10), ns
Vineland						
Communication	100 (15)	80.3 (14.1)	−6.4 (20)	.001‡	–	–
Daily living	100 (15)	83.5 (16.5)	−4.6 (20)	.001‡	–	–
Socialization	100 (15)	81.1 (14.8)	−5.8 (20)	.001‡	–	–

ns, Not significant; *t(df)*, Student *t*(distribution function).

*$P < .05$.

†$P < .01$.

‡$P < .001$.

TABLE E2. PedsQL scores of the HLH group compared with cancer group data

Measure	HLH group, mean (SD)	Cancer group, mean (SD)	t(df)	*P* value
Physical	68.3 (18.1)	75.0 (18.8)	−1.4 (13)	.190
Psychosocial	58.7 (15.7)	63.5 (21.7)	−2.4 (13)	.031*
Total	62.1 (13.7)	71.0 (17.0)	−2.4 (13)	.029*

t(df), Student *t*(distribution function).
*$P < .05$.

TABLE E3. Teacher-rated SDQ results for the HLH group compared with normative data

	TSDQ HLH group (n = 18)		TSDQ UK normative data (n = 8208)			
	Mean	**SD**	**Mean**	**SD**	**t(df)**	***P* value**
SDQ						
Total	11.4	7.9	6.6	6.0	2.6 (17)	.019*
Emotional	2.6	2.4	1.4	1.9	2.1 (17)	.047*
Conduct	1.0	1.5	0.9	1.6	0.3 (17)	.780
Hyperactivity	4.8	4.1	2.9	2.8	2.0 (17)	.067
Peer relationships	3.1	2.7	1.4	1.8	2.6 (17)	.020*
Impact	1.9	2.2	0.4	1.0	2.8 (17)	.021*

Note: Higher scores indicate greater difficulties.
t(df), Student *t*(distribution function), *TSDQ*, teacher version of the SDQ.
*$P < .05$.