Table 2. Univariate Analysis of the Incidence of CH with the Frequency and Probability of Developing CH by the Kaplan-Meier Test

Category	N	CH Incidence, n (%)	P Value[a]	Probability, %	P Value[b]
Total	68	28 (41.2)		61.5 ± 9.1	
Sex					
Female	33	16 (48.5)	NS	70.9 ± 11.2	NS
Male	35	12 (34.3)		75.6 ± 18.4	
Primary disease					
Malignant	44	26 (59.1)	<.001	75.6 ± 8.6	<.001
Nonmalignant	24	2 (8.3)		6.2 ± 6.1	
Type of transplantation					
Autologous	7	4 (57.1)	NS	61.9 ± 19.9	NS
Allogeneic	61	24 (39.3)		61.7 ± 10.8	
Age at HSCT, years					
<10	41	14 (34.2)	NS	56.8 ± 12.8	<.05
≥10	27	14 (51.9)		72.1 ± 11.3	
Age at first radiation, years					
<10	28	16 (57.1)	NS	68.1 ± 11.0	NS
≥10	21	12 (57.1)		75.8 ± 11.8	
Total cranial radiation dose, Gy					
0	19	0 (0)	<.001	0	<.001
6-12	39	18 (46.2)		62.0 ± 10.1	
18-30	10	10 (100)		100	

NS indicates not significant.
[a]Pearson's χ square test or Fisher exact test.
[b]Log-rank test (Kaplan-Meier).

a significantly higher probability of developing CH (75.6% ± 8.6% versus 6.2% ± 6.1%; $P < .001$).

Age at HSCT showed a marginally significant effect. Patients who underwent HSCT at age ≥15 years had a slightly higher probability of developing CH than did younger patients (56.8% ± 12.8% versus 72.1% ± 11.3%; $P < .05$). The mean total cranial radiation dose was 8.8 ± 8.4 Gy in patients aged 0 to 9 years and 12.8 ± 8.5 Gy in those aged ≥10 years ($P = .058$).

The patients were divided into three groups according to total cranial radiation dose: group A, none (n = 19); group B, 6 to 12 Gy (n = 39); and group C, 18 to 36 Gy (n = 10). CH was not detected in any of the group A patients but was found in 46.2% of the group B patients and in 100% of the group C patients; the intragroup differences were highly significant ($P < .001$) (Table 2). The probability of CH was 0% in group A, 62.0% ± 10.1% in group B, and 100% in group C ($P < .001$) (Table 2 and Figure 2B).

The results of Cox multivariate regression analysis for developing CH are presented in Table 3. Of the covariates shown to be significant in univariate analysis, only cranial radiation dose was found to be significantly associated with CH risk ($P < .001$).

CH Score and Grade

In the 28 patients with CH, the total CH score at the latest MRI ranged from 1 to 19 points (median, 5 points). The total number of CH lesions in these patients was 115, including 75 lesions with a CH score of 1, 27 with a CH score of 2, four with a CH score of 3, and four with a CH score of 5. Only 21 of the 115 lesions that were identified by T2*-weighted MRI (18.3%) were visible on conventional T2-weighted MRI. In particular, conventional T2-weighted MRI could identify all nine lesions with a CH score of 3 or 4 but none of lesions with a CH score of 1 or 2.

The most common location of CH was supratentorial (n = 102; 88.7%), particularly in the

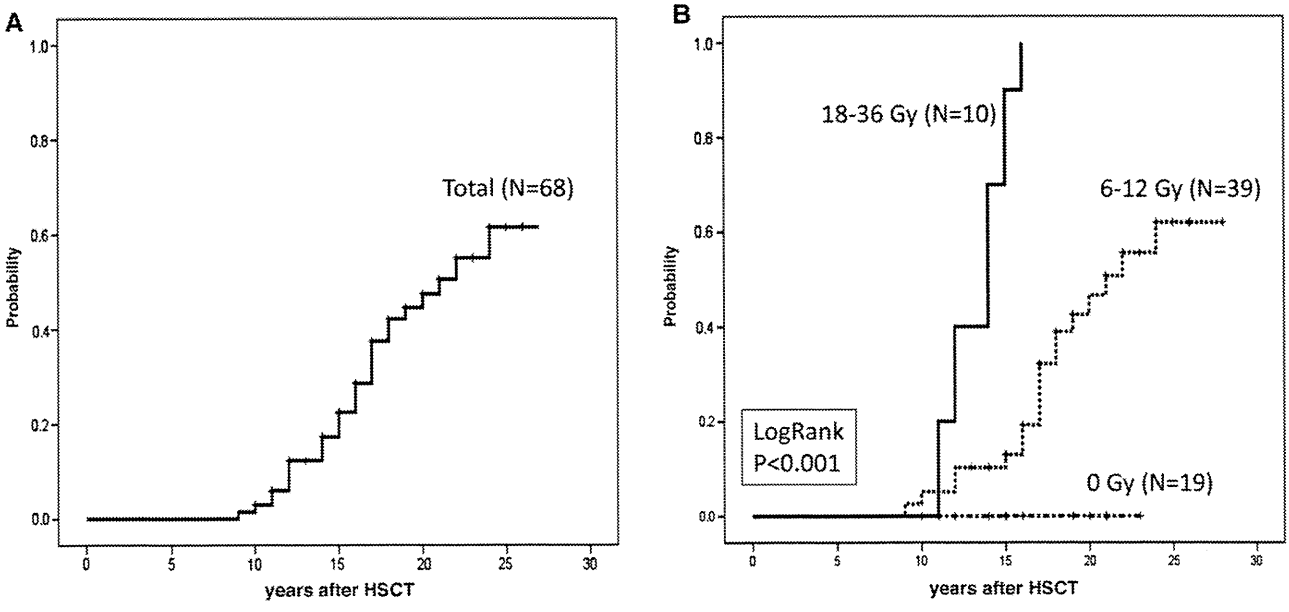

Figure 2. Probabilty of developing CH after HSCT. (A) The probability of developing CH in the 68 study patients was 61.5% ± 9.1% at 25 years after HSCT. (B) Based on total cranial radiation dose, the probability was 0% in the patients who did not receive irradiation to the head before and/or during the conditioning treatment for HSCT, 62.0% ± 10.1% in those with a total cranial radiation dose of 6 to 12 Gy, and 100% in those with a total dose of 18 to 36 Gy. These differences are highly significant ($P < .001$).

Table 3. Cox Multivariate Regression Analysis for Developing CH

	HR[a]	95% CI	P Value
Disease (malignant versus nonmalignant)	2.02	0.45-9.05	.360
Age at transplantation (<10 years versus ≥10 years)	1.37	0.62-3.02	.435
Cranial radiation dose (0 versus 6-12 versus 19-36 Gy)	10.02	3.65-27.49	<.001

[a]Hazard ratio.

frontal and parietal lobes, and CH was prevalent in subcortical and deep white matter (Table 4). Only 13 infratentorial and basal ganglia lesions (11.3%) were identified, most of which were in the cerebellum (10 of 13; 76.9%) (Table 5).

A significant correlation was found between the latest total CH score and the total cranial radiation dose (Figure 3). Neither age at HSCT nor age at the first irradiation treatment were correlated with CH score (data not shown). CH grade was 0 in 40 patients, I in 14 patients, II in eight patients, III in four patients, and IV in one patient.

Changes in CH Score During the 5-Year Observation Period

CH was identified on the initial MRI in 22 patients, and was newly identified in six patients during the 5-year observation period. Mixed high and low signals on T1- and T2-weighted imaging with or without surrounding edema that had been absent in previous MRI images were newly identified in six patients.

Changes in total CH score according to time after initial brain irradiation treatment are shown in Figure 4. Over the 5-year observation period, 23 of the 28 patients (82.1%) had an increase in total CH score, by 1-10 points. Three patients exhibited a transient increase in total CH score, possibly reflecting artifacts of T2*-weighted MRI. In terms of grading classification, three patients progressed from grade I to grade II, and three progressed from grade II to grade III during the 5-year observation period.

Table 4. Supratentorial Localization of CH Lesions

CH Score	Frontal Lobe	Temporal Lobe	Parietal Lobe	Occipital Lobe	Total
Cerebral cortex					
1	1	2	3	3	9
2	3		2	1	6
3					
4		1			1
Subtotal	4	3	5	4	16
Subcortical white matter					
1	15	5	12	3	35
2	6		5		11
3			1		1
4		1			1
Subtotal	21	6	18	3	48
Deep white matter					
1	12	3	7	2	24
2	1	1	1	1	4
3					
4					
Subtotal	13	4	8	3	28
Periventricular white matter					
1	4		2	1	7
2	2				2
3	1				1
4					
Subtotal	7	0	2	1	10
Total					
1	32	10	24	9	75
2	12	1	8	2	23
3	1		1		2
4		2			2
Total	45	13	33	11	102

Table 5. Localization of Infratentorial and Basal Ganglia CH Lesions

CH Score	Basal Ganglia	Thalamus	Midbrain	Pons	Cerebellum	Total
1		1		1	2	4
2					4	4
3					2	2
4	1				2	3
Total	1	1	0	1	10	13

Clinical Symptoms

Two patients experienced episodes of vertigo and headache and bleeding from CH at the cerebellum that was diagnosed by conventional MRI at other hospitals. CH grade was I (total score 4) in one of these patients and III (total score 15) in the other. One patient had frequent headaches and CH (grade III; total score 15) detected just before enrolling in this study. Another patient had hand numbness and was diagnosed with CH (grade IV, total score 6) at our hospital, where MRI and computed tomography (CT) scan revealed a giant CH in the right basal ganglia (Figure 5). Consultation with a neurosurgeon resulted in periodical MRI examinations and careful follow-up. Exacerbation of symptoms has not been observed during the subsequent 5 years, but the patient's total CH score increased from 6 to 7 because of a new lesion found in the left frontal lobe. All other patients with CH lesions detected in this study were asymptomatic throughout the follow-up period.

Venous Angioma

Venous malformation or angioma was not detected on contrast MRI with gadolinium-chelates in any of the patients with or without CH changes.

DISCUSSION

RICH of the brain was first recognized as a late effect of radiation therapy for brain tumors using high-dose irradiation (50-60 Gy). This effect is commonly seen in children treated with radiation therapy for reasons other than brain tumors. Progress in diagnostic

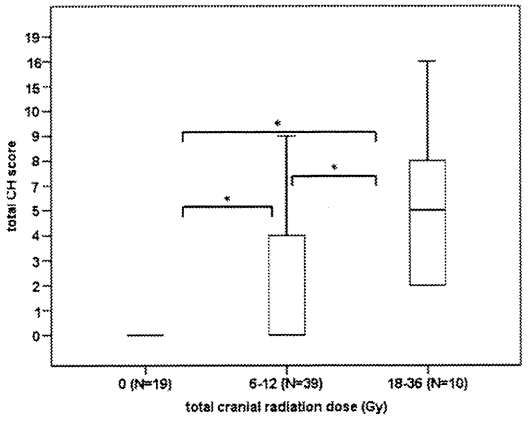

Figure 3. Total CH scores according to total cranial radiation dose before and/or during conditioning treatment for HSCT. Total CH scores between 0 Gy and 6-12 Gy, between 0 Gy and 18-36 Gy, and between 6-12 Gy and 18-36 Gy were statistically significantly different. *$P < .001$, Mann-Whitney *U* test.

techniques, such as MRI, has contributed to the early detection of RICH. However, little is known about the incidence, dose relationship, localization, natural course, and clinical symptoms in HSCT recipients, in whom radiation is often used as a part of chemotherapy for leukemia or as TBI in conditioning.

Strenger et al [15] reported that eight of 171 pediatric patients who underwent cranial radiation at 9 to 85.6 Gy at age 10.5 months to 38.5 years (median, 8.3 years) developed CH at 2.9 to 18.4 years after irradiation, with a cumulative incidence of 6.74% at 20 years after radiation therapy. In that study, CT or conventional MRI without T2*-weighted imaging was used to diagnose CH. Koike et al [16] reported that 18 of 90 children (20%) who had received 18 to 66 Gy of cranial radiation at age 0-17 years (mean, 7.2 ± 4.5 years) developed CH at 2 to 10 years after the initial irradiation.

In the present study, 28 of 68 long-term adult survivors of childhood HSCT (41.2%) were diagnosed with CH, and the probability of developing CH by 25 years after HSCT was 61.5% ± 9.1%. Given that the incidence of intracranial cavernous malformations is approximately 0.5% in the general population, the frequency and probability in our series apparently exceed this range. Because CH was not found in patients who had not received radiation to the head before and/or during the conditioning regimen for HSCT, radiation was considered the cause of CH in those survivors.

CH was found in no patients who did not receive cranial radiation (n = 19), in 46.2% of those who received 6 to 12 Gy (n = 39), and in 100% of those who received 18 to 36 Gy (n = 10). Thus, 6 to 12 Gy might be considered the threshold level for development of RICH, and higher radiation dose was significantly associated with a higher frequency of RICH.

Younger age has been reported as a risk factor for RICH by several authors. However, this association with younger age was not found in the present study, and CH developed at a slightly higher frequency in children aged >15 years at the time of radiation therapy. This higher incidence in the oldest age group was considered related to the higher total cranial radiation dose received by this group.

Naturally occurring CH is known to be associated with developmental venous malformation (DVM) or angioma (DVA), which is usually occult and detected during surgery or at autopsy, with a crude detection rate of 0.43 per 100,000 adults per year [17]. Abdulrauf et al [18] reported DVM in 24% of patients with CH, and DVA is reportedly associated with cavernous malformation in 8% to 33% of cases [19]. DVA was not found in our patients on contrast MRI; susceptibility-weighted MRI might be more sensitive for detecting DVA. Thus, the causative association of DVM and CH is less likely in our patients.

Cox multivariate regression analysis identified cranial radiation dose as the sole factor affecting the development of CH in our analysis. However, other factors, such as intrathecal therapy or certain chemotherapies, might have contributed to the development of late changes in neurologic function and may be related to the imaging changes to some extent. We could not analyze such factors, however, because we could not collect all of these data from the referring hospitals.

T2*-weighted MRI was sensitive and useful in the early detection of CH. Maeda et al [20] judged

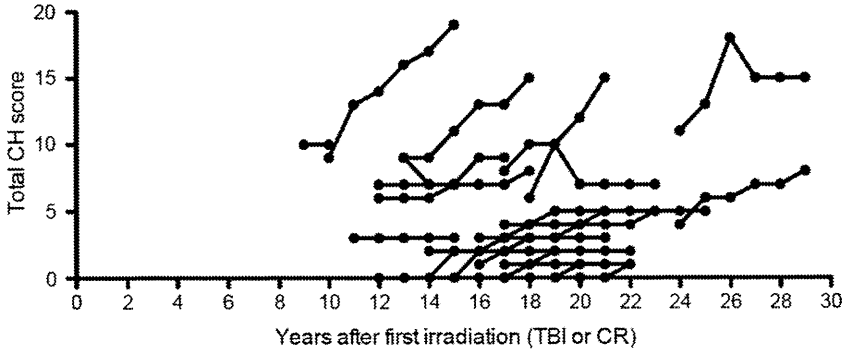

Figure 4. Changes in total CH scores during the 5-year observation period in the patients who developed RICH.

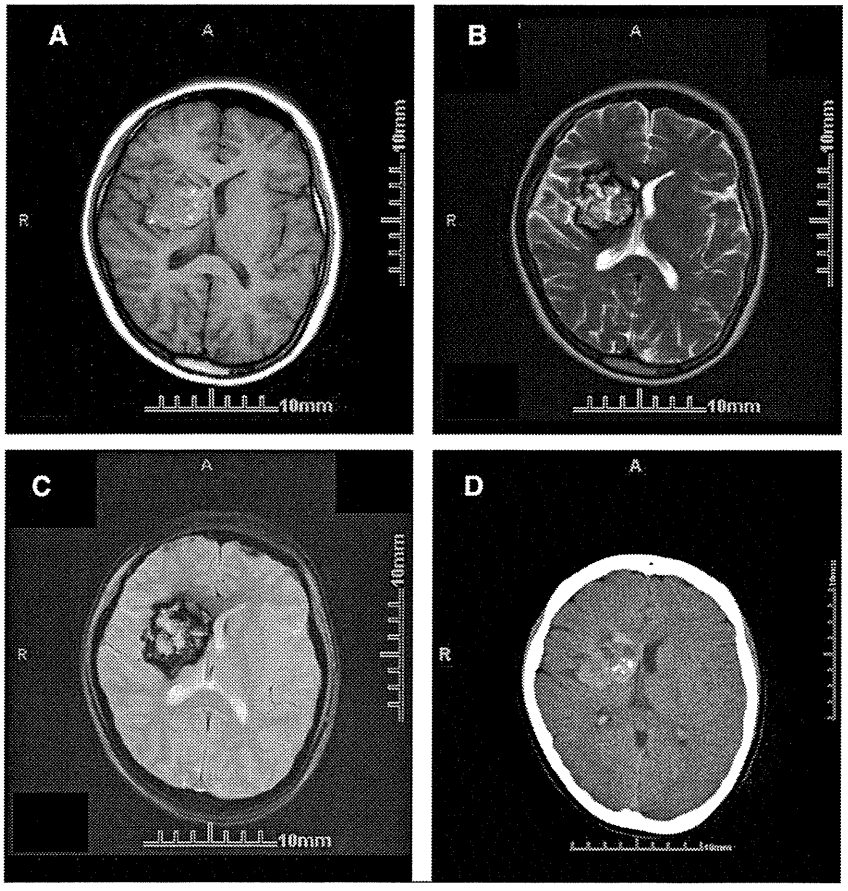

Figure 5. MRI and CT images in a patient with a giant CH. (A) T1-weighted MRI. (B) T2-weighted MRI. (C) T2*-weighted MRI. (D) CT.

T2*-weighted MRI superior to conventional T2-weighted MRI in detecting the number and distribution of lesions in CH. In our analysis, small lesions were identified only on T2*-weighted imaging, not on conventional T2-weighted imaging, likely contributing to the higher incidence in the present study compared with previous reports.

The onset of CH detected by T2*-weighted MRI ranged from 9 to 24 years after HSCT and also from 9 to 24 years after the first radiation treatment, whereas diagnosis of CH by conventional T2-weighted MRI was delayed or not possible in most cases. Because CH changes were already present in most survivors at the time of initial MRI, actual onset was considered to be earlier. Thus, the present study has a limited ability to precisely detect the onset of RICH.

As in previous reports of RICH, the most common localization of hemangioma was supratentorial, particularly in the subcortical and deep white matter. Infratentorial lesions were found predominantly in the cerebellum, which might have caused clinical symptoms, such as vertigo or headache, in a few patients.

The CH scoring system that we have developed is useful for quantifying lesions and evaluating changes occurring during the follow-up period. Increased CH scores were seen in 23 of 28 patients (82.1%) during the 5-year observation period. Thus, this study reveals details of the course and speed of CH growth through annual follow-up examinations. The use of this scoring method could also provide insight into the pathogenesis and natural course of RICH, although the method's clinical relevance remains uncertain given the small number of patients and short follow-up period of the present study.

In general, RICH lesions neither disappear nor diminish over their natural course. However, a decrease in CH score after a transient increase was seen in three patients during the study period. This transient increase in CH score was considered related to an artifact of T2*-weighted MRI. Evaluation by single-time point MRI may carry a risk of overestimation, and thus careful evaluation by serial MRI over sufficient intervals is necessary.

Despite the progression of some CH lesions, most patients remained asymptomatic, as in previous reports. Newly recognized signal changes on T1- and T2-weighted MRI with or without surrounding edema of preexisting CH are considered to reflect bleeding episodes during the intervals between examinations, and repeated bleeding may finally form a mass lesion. Symptomatic bleeding may occur with or without triggers that cause a rapid increase in blood pressure,

however. Pregnancy and labor are known risk factors for such bleeding [21], probably because the angiogenic process is initiated by growth factors, such as vascular endothelial growth factor, basic fibroblast growth factor, and placental growth factor [22]. We treated a case of seizure caused by CH bleeding during labor in a 31-year-old female who had a history of cranial radiation of 18 Gy for acute lymphoblastic leukemia in childhood. Her CH grade was IV with a mass effect at the right parahippocampal gyrus, and her total CH score was 23. This patient was not included in the present study because she had no history of HSCT.

We suggest that MRI, including T2*-weighted imaging, should be routinely and serially performed over the long term in those who have received radiation to the head during childhood or adolescence. Attention should also be given to patients in whom RICH was identified, especially those with grade III/IV CH, regardless of the localization of lesions, or those with grade I/II CH with infratentorial lesions, given that infratentorial CH is more closely associated with symptomatic bleeding compared with supratentorial CH [23,24]. Information on the presence of RICH will aid accurate diagnosis in those survivors and facilitate proper management in the event of clinical bleeding episodes. Surgical indications in those with repeated bleeding episodes and progressive neurologic symptoms should be discussed with a neurosurgeon.

Routine and serial MRI is useful for early detection of other well-recognized brain imaging changes, such as mineralizing microangiopathy, leukoencephalopathy, and brain tumors [25]. Meningioma was detected in eight patients with cranial radiation (five with RICH and three without RICH), and oligoastrocytoma was detected in one patient with cranial radiation and RICH and will be reported separately.

Although we have clarified the high incidence and the importance of RICH in adult long-term survivors of HSCT performed during childhood in a single-center study, the mechanisms of RICH remain unknown. Retrospective and multicenter studies using sensitive T2*-weighted MRI on long-term survivors of childhood cancer who received radiation to the skull should be planned to confirm the actual incidence of RICH in a larger population. Prospective and long-term studies on those who received radiation to the head during treatment are needed to examine the onset and natural course of RICH.

In conclusion, because all of our patients with CH had a history of radiation therapy to the brain, and because none of the patients who did not receive radiation therapy developed CH, the cause of CH in those adult survivors of childhood HSCT was considered to be radiation. We found a dose-reponse relationship between total cranial radiation and the development of CH and determined that the radiation dose of 6 to 12 Gy commonly used in patients undergoing HSCT could cause RICH. Careful and long-term evaluation with MRI, including T2*-weighted imaging, is strongly recommended in HSCT recipients who received radiation therapy before and/or during HSCT. This is the first report of a high prevalence of RICH among long-term HSCT survivors, in which radiologic changes were quantitatively and longitudinally evaluated by annual MRI, including T2*-weighted imaging.

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REFERENCES

1. Robison LL, Armstrong GT, Boice JD, et al. The Childhood Cancer Survivor Study: a National Cancer Institute–supported resource for outcome and intervention research. *J Clin Oncol.* 2009;27:2308-2318.
2. Leisenring WM, Mertens AC, Armstrong GT, et al. Pediatric cancer survivorship research: experience of the Childhood Cancer Survivor Study. *J Clin Oncol.* 2009;27:2319-2327.
3. Oeffinger KC, Mertens AC, Sklar CA, et al. Chronic health conditions in adult survivors of childhood cancer. *N Engl J Med.* 2006;355:1572-1582.
4. Committee for Nationwide Survey Data Management. Transplant activity report. In: Imamura M, Hara M, Sakamaki H, Kato K, Mitamura M, Tanaka J, Hiraoka A, Adachi S, Kato S, Yabe H, Kawa K, Morishima Y, Takanashi M, Nagamura T, Suzuki R, editors. *Annual Report of Nationwide Survey 2010. Monograph*, Vol.29. Nagoya: The Japan Society for Hematopoietic Cell Transplantation; 2011. p. 3-80.
5. Ishida Y, Honda M, Ozono S, et al. Late effects and quality of life of childhood cancer survivors, part 1: impact of stem cell transplantation. *Int J Hematol.* 2010;91:865-876.
6. Hudson MM, Mulrooney DA, Bowers DC, et al. High-risk populations identified in Childhood Cancer Survivor Study investigations: implications for risk-based surveillance. *J Clin Oncol.* 2009;27:2405-2414.
7. Ishiguro H, Yasuda Y, Hyodo H, et al. Growth and endocrine function in long-term adult survivors of childhood stem cell transplant. *Clin Pediatr Endocrinol.* 2009;18:1-14.
8. Ishiguro H, Yasuda Y, Tomita Y, et al. Long-term follow-up of thyroid function in patients who received bone marrow transplantation during childhood and adolescence. *J Clin Endocrinol Metab.* 2004;89:5981-5986.
9. Ishiguro H, Yasuda Y, Tomita Y, et al. Gonadal shielding to irradiation is effective in protecting testicular growth and function in long-term survivors of bone marrow transplantation during

childhood or adolescence. *Bone Marrow Transplant.* 2007;39: 483-490.
10. Kim DS, Park YG, Choi JU, et al. An analysis of the natural history of cavernous malformations. *Surg Neurol.* 1997;48:9-17.
11. Ciricillo SF, Cogen PH, Edwards MS. Pediatric cryptic vascular malformations: presentation, diagnosis and treatment. *Pediatr Neurosurg.* 1994;20:137-147.
12. Keezer MR, Del Maestro R. Radiation-induced cavernous hemangiomas: case report and literature review. *Can J Neurol Sci.* 2009;36:303-310.
13. Heckl S, Aschoff A, Kunze S. Radiation-induced cavernous hemangiomas of the brain. *Cancer.* 2002;94:3285-3291.
14. Liu Y, Preston R, Thomas SM, et al. Cerebral cavernoma: an emerging long-term consequence of external beam radiation in childhood. *Clin Endocrinol.* 2010;73:555-560.
15. Strenger V, Sovinz P, Lackner H, et al. Intracerebral cavernous hemangioma after cranial irradiation in childhood: incidence and risk factors. *Strahlenther Onkol.* 2008;184:276-280.
16. Koike S, Aida N, Hata M, et al. Asymptomatic radiation-induced telangiectasia in children after cranial irradiation: frequency, latency, and dose relation. *Radiology.* 2004;230:93-99.
17. Al-Shahi R, Bhattacharya JJ, Currie DG, et al. Prospective, population-based detection of intracranial vascular malformations in adults: the Scottish Intracranial Vascular Malformation Study (SIVMS). *Stroke.* 2003;34:1163-1169.
18. Abdulrauf SI, Kaynar MY, Awad IA. A comparison of the clinical profile of cavernous malformations with or without associated venous malformations. *Neurosurgery.* 1999;44:41-46.
19. Rabinov JD. Diagnostic imaging of angiographically occult vascular malformations. *Neurosurg Clin North Am.* 1999;10: 419-432.
20. Maeda K, Terashima T, Kawai H, et al. T2*-weighted MR images of a patient with familial cerebral cavernous malformation. *Intern Med.* 2007;46:541-542.
21. Savi-Abbasi S, Feiz-Erfan I, Spetzler R, et al. Hemorrhage of cavernous malformations during pregnancy and in the peripartum period: causal or coincidence? *Neurosurg Focus.* 2006;21:E12.
22. Zygmunt M, Herr F, Munstedt K, et al. Angiogenesis and vasculogenesis in pregnancy. *Eur J Obstet Gynecol Reprod Biol.* 2003; 110(suppl 1):S10-S18.
23. Abla AA, Turner JD, Mitha AP, et al. Surgical approaches to brainstem cavernous malformations. *Neurosurg Focus.* 2010; 29:E8.
24. Porter PJ, Willinsky RA, Harper W, et al. Cerebral cavernous malformations: natural history and prognosis after clinical deterioration with or without hemorrhage. *J Neurosurg.* 1997;87: 190-197.
25. Vazques E, Lucaya J, Castellote A, et al. Neuroimaging in pediatric leukemia and lymphoma: differential diagnosis. *Radiographics.* 2002;22:1411-1428.

X-linked lymphoproliferative disease due to SAP/SH2D1A deficiency: a multicenter study on the manifestations, management and outcome of the disease

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X-linked lymphoproliferative disease (XLP1) is a rare immunodeficiency characterized by severe immune dysregulation and caused by mutations in the *SH2D1A*/SAP gene. Clinical manifestations are varied and include hemophagocytic lymphohistiocytosis (HLH), lymphoma and dysgammaglobulinemia, often triggered by Epstein-Barr virus infection. Historical data published before improved treatment regimens shows very poor outcome. We describe a large cohort of 91 genetically defined XLP1 patients collected from centers worldwide and report characteristics and outcome data for 43 patients receiving hematopoietic stem cell transplant (HSCT) and 48 untransplanted patients. The advent of better treatment strategies for HLH and malignancy has greatly reduced mortality for these patients, but HLH still remains the most severe feature of XLP1. Survival after allogeneic HSCT is 81.4% with good immune reconstitution in the large majority of patients and little evidence of posttransplant lymphoproliferative disease. However, survival falls to 50% in patients with HLH as a feature of disease. Untransplanted patients have an overall survival of 62.5% with the majority on immunoglobulin replacement therapy, but the outcome for those untransplanted after HLH is extremely poor (18.8%). HSCT should be undertaken in all patients with HLH, because outcome without transplant is extremely poor. The outcome of HSCT for other manifestations of XLP1 is very good, and if HSCT is not undertaken immediately, patients must be monitored closely for evidence of disease progression. (*Blood*. 2011;117(1):53-62)

Introduction

X-linked lymphoproliferative disease (XLP) is a rare primary immunodeficiency first described in 1975 by Purtilo[1] and characterized by severe immune dysregulation often after viral infection (typically with Epstein-Barr virus [EBV]). Since XLP was first

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described, our understanding of the molecular and cellular pathogenesis of the disease has greatly improved. However, clinically, it is still difficult to determine optimal management and prognosis for patients due to the variability of clinical presentation, lack of genotype-phenotype correlation, and rarity of the disease. Purtilo established an XLP registry in 1980, and by 1995 more than 270 boys had been identified in 80 kindreds.[2] To date this registry has provided the only data on clinical phenotype and prognosis for this patient group. Overall mortality in this group was 75%, with 70% of boys succumbing before 10 years of age. However, current outcomes for XLP may be very different due to the availability of unambiguous molecular diagnosis, improved viral monitoring, and the improvement in treatment regimens for disease manifestations.

XLP affects 1 to 3 million boys,[3,4] and most commonly presents in childhood or early adolescence. Presentation may be acute in the case of fulminant infectious mononucleosis (FIM)/hemophagocytic lymphohistiocytosis (HLH) or lymphoma or less aggressive with dysgammaglobulinemia or recurrent infections. Patients often manifest more than one phenotype and may progress from one phenotype to another, for example presenting with hypogammaglobulinemia and progressing to lymphoma, and different clinical features are often present in families highlighting the lack of genotype-phenotype correlation. Other rare but well-described presenting features include aplastic anemia, vasculitis, and chronic gastritis.[2,5-8] It is now known that the clinical syndrome of XLP arises from 2 different genetic defects in *SH2D1A* (XLP1, by far the most common and the focus of this report) and the *BIRC/XIAP* gene (XLP2). The gene responsible for XLP1 is the *SH2D1A* gene found on the X chromosome at position Xq25,[9-11] which encodes the cytoplasmic protein SAP (signaling lymphocyte activation molecule or SLAM-associated protein). SAP is a key regulator of normal immune function in T cells,[12-14] natural killer (NK) cells,[15-18] NKT cells,[19,20] and possibly B cells,[21] and defects in this protein lead to the varied immune defects described in XLP1 patients.[20,22] Humoral defects seen in this disease are thought to arise from impaired $CD4^+$ T-cell interaction with B cells and not an intrinsic B-cell deficit.[23]

Although it has always been presumed that EBV infection plays a crucial role in the development of clinical features in XLP1 patients, it is now clear that a proportion of boys are EBV negative at presentation and remain so. Indeed, 10% of patients have immunological abnormalities before any evidence of EBV exposure.[4,24] XLP1 is therefore a disorder of immune dysregulation rather than a disorder specifically associated with EBV infection.

Before 1994, acute management of FIM and HLH included antiviral medications, high-dose intravenous immunoglobulin (Ig), immunosuppressants, and other immune modulators such as interferon-α. These treatments proved disappointing[25] and the XLP registry data showed a survival of only 4% for boys presenting with these manifestations. Improved chemotherapy regimes for lymphoma and immunosuppressive protocols to treat HLH (including rituximab) may reduce the mortality rate for XLP1 patients and allow stabilization before hematopoietic stem cell transplant (HSCT).[26] Our report provides valuable outcome data collected since the introduction of current HLH treatment protocols, focusing on XLP1 patients with mutations in the *SH2D1A* gene.

Allogeneic HSCT remains the only curative option for XLP1 at present although large scale outcome studies are not available. Recently, Lankester et al reviewed 14 cases in the literature who had undergone HSCT and found an overall survival of 71% (10/14) with little evidence of EBV reactivation and posttransplant lymphoproliferative disease.[27] We describe here outcome data for a much larger cohort of patients transplanted since 1997.

There is no consensus on whether clinically stable XLP1 patients should undergo HSCT as the natural history of the disease is so variable, even within the same family. Treatment and management of the disease is severely hampered by the lack of data of a large cohort of patients and previously published outcome data are based on historical data, which may represent patients with conditions other than XLP1 as inclusion was based on clinical and not genetic diagnosis. Also, little recent data exist for patients who remain untransplanted. Hence, we describe a large cohort of genetically defined XLP1 patients collected from centers worldwide. The data presented will allow for better counseling of affected families regarding prognosis and management options, particularly in relation to timing of transplant.

Methods

Data collection

Questionnaires regarding patient demographics, transplant characteristics, and outcome were sent to centers worldwide identified through the European Society for Immunodeficiencies/European Bone Marrow Transplantation Registry, published case reports or centers known to perform pediatric HSCT. Retrospective analysis was performed using data collected for 91 patients from 32 centers worldwide. The number of cases from each center varied between 1 and 27 but was on average 1-2 cases. Patients included in this study were born between 1941 and 2005; 63 were born in or after 1990 (24 untransplanted patients and 39 transplanted patients). Only patients with a confirmed mutation in the *SH2D1A* gene were included in this series. Patients with mutations in other XLP-associated genes such as *XIAP/BIRC-4* were excluded, as were patients with abnormal SAP expression but no confirmed mutation in *SH2D1A*. EBV status was determined by polymerase chain reaction to avoid variable serology results in XLP1 patients and especially in those with dysgammaglobulinemia. Questionnaires offered reporting of FIM and HLH separately; thus, some centers with experience in this area reported patient data accordingly, and it is presented as such.

Data in various forms from 11 patients have been previously published[5,27-32] but standardized information was recollected in this study and added to the series.

Management of HLH and lymphoma

Patients who presented with HLH were managed predominantly in accordance with HLH 94 or HLH 2004 protocols. Additional or alternative treatment included antiviral therapy (aciclovir, ganciclovir, or foscarnet, n = 6), high-dose intravenous immunoglobulin (n = 9), immunosuppression (steroids, cyclosporine, and etoposide, n = 12), or anti-CD20 antibody (rituximab, n = 10). Intrathecal therapy was used where central nervous system involvement was suspected. Ten patients who proceeded to transplant received rituximab therapy before transplant, either as treatment for HLH or during conditioning.

Regimes for the treatment of lymphoma varied in line with appropriate national guidelines (eg, COPAD [cyclophosphamide, vincristine, prednisone, and doxorubicin]) study, Berlin-Frankfurt-Munster Group, Associazione Italiana Ematologia Oncologia Pediatrica, or United Kingdom Children's Cancer Study Group guidelines) and only occasionally involved surgical management.

Statistical analysis

Kaplan-Meier curves were used to analyze survival figures. The log rank test (Mantel-Cox) and Gehan-Breslow-Wilcoxon tests were used to compare survival between different groups. Statistical analysis including hazard ratio calculation was performed using GraphPad Prism Version 5.00 for Windows.

Table 1. Presenting symptoms and features of XLP1 patients with associated mortality

	Incidence	Mortality
Presenting symptom		
HLH	31.9%	65.5%
FIM	7.7%	14.3%
Lymphoma	14.3%	7.7%
Dysgammaglobulinemia	22%	5%
Family history of XLP1 alone	16.5%	20%
Other	7.7%	14.3%
Features occurring at any time		
HLH	35.2%	65.6%
FIM	9.9%	22.2%
Lymphoma	24.2%	9%
Dysgammaglobulinemia	50.5%	13%
Other	15.4%	28.6%

Results

Data from 91 patients (64 pedigrees) in 32 centers worldwide were included in this report. The overall survival of XLP1 patients was 71.4% (65/91), and patients displayed a heterogeneous clinical phenotype. Due to the heterogeneity of the group, data were analyzed according to presentation with HLH, EBV status, and whether patients had received HSCT, allowing characterization of outcome after transplant.

Spectrum of XLP1 mutations

In keeping with previous publications, no genotype/phenotype correlation was evident, and the most frequently reported mutation involved the arginine residue at position 55 (exon 2) found in 11 patients from 9 different families. Detailed genetic information was available for 62 patients (50 pedigrees; supplemental Table 1, available on the *Blood* Web site; see the Supplemental Materials link at the top of the online article). Exon 2 had the most mutations with missense mutations accounting for the majority but nonsense, frameshift, and splice site mutations were also reported. Large gene deletions (up to 11 Mb) including those involving the whole gene were identified in 5 families. Three of these larger deletions were associated with gastrointestinal symptoms of colitis and gastritis. Such symptoms were not found in patients with other mutations apart from a patient with diarrhea as a feature (missense mutation exon 1, 62 T > C). In a further 29 patients, detailed genetic data were not supplied but a SAP/*SH2D1A* gene defect was confirmed by the documenting center.

Clinical manifestations of XLP1

Table 1 shows the presenting features of disease as well as features of disease manifesting throughout the course of the condition. HLH remained the most common presenting feature (39.6%), although dysgammaglobulinemia was the manifestation seen most commonly in patients during the course of the illness.

Although clinical features have remained similar to previously published data,[2] the survival associated with XLP1 is 71.4%, which is significantly improved over historical survival of 25%. The survival associated with different phenotypes has also changed significantly with mortality associated with HLH decreased from 96% to 65%, lymphoproliferative disease from 35% to 8%, and dysgammaglobulinemia from 55% to 5%.

Twenty-two patients suffered from malignant lymphoproliferative disease, with eighteen patients (81.8%) diagnosed with B-cell non-Hodgkin lymphoma mainly of the abdomen and cervical region. In 5 patients the disease was recurrent, with 1 patient experiencing a cerebral tumor. Only 1 patient was reported with cerebral T-cell lymphoma. Data on tumor histology is lacking in 3 patients.

Immunological abnormalities at diagnosis

Details of immune function were available for 57 patients, although in some cases, data were only available after the onset of disease manifestations that may have influenced immunoglobulin and lymphocyte subset levels. Immunoglobulin levels were recorded in 49 patients, and 32 of these showed varying degrees of abnormal immunoglobulin levels. Twelve children presented with neutropenia. Lymphocyte subset data were available for 47 patients; 19 showed a reduced percentage of B cells, 26 showed low NK cell numbers, and 12 had a reversed CD4:CD8 ratio.

Presentation with HLH

The mortality for patients presenting with HLH was 65.6%, with a median age at presentation of 3 years 2 months (range 8 months to 9 years). Of the 32 patients with HLH, 16 underwent transplant, of whom 8 survived (50%; Figure 1). Of those who did not receive a transplant, only 3 survived (18.8%), confirming previous reports that the prognosis for patients with HLH associated with a genetic defect is extremely poor and that HSCT is necessary.

EBV status

EBV status was documented in 79 patients showing that 51 (64.6%) were EBV positive at presentation or diagnosis (Table 2 and supplemental Figure 1). The median age of presentation in this group was 4 years (range 8 months to 40 years), and the overall mortality was 35.2% (18/51). There was no significant difference in mortality between patients with (35.2%) and without (28.6%) documented EBV infection.

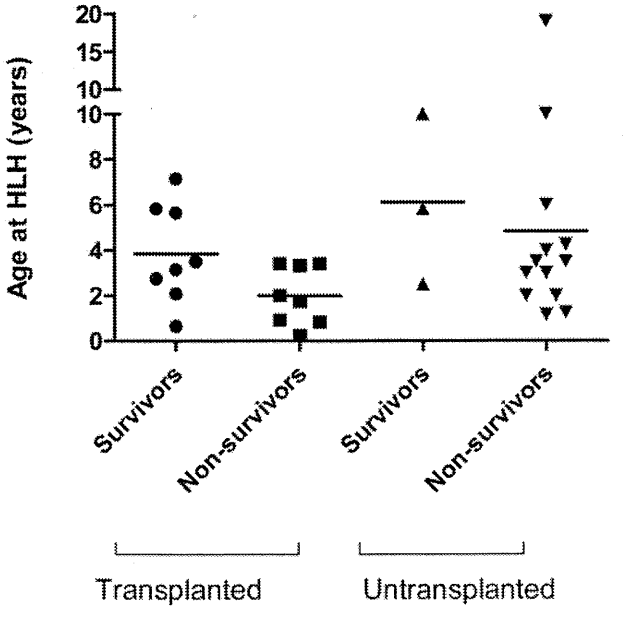

Figure 1. Outcome of patients with HLH during course of disease. Survival of patients who present with HLH—patients who remain untransplanted have a poor survival outcome with only 18.8% survival. By contrast the survival of those who undergo transplant is higher at 50%.

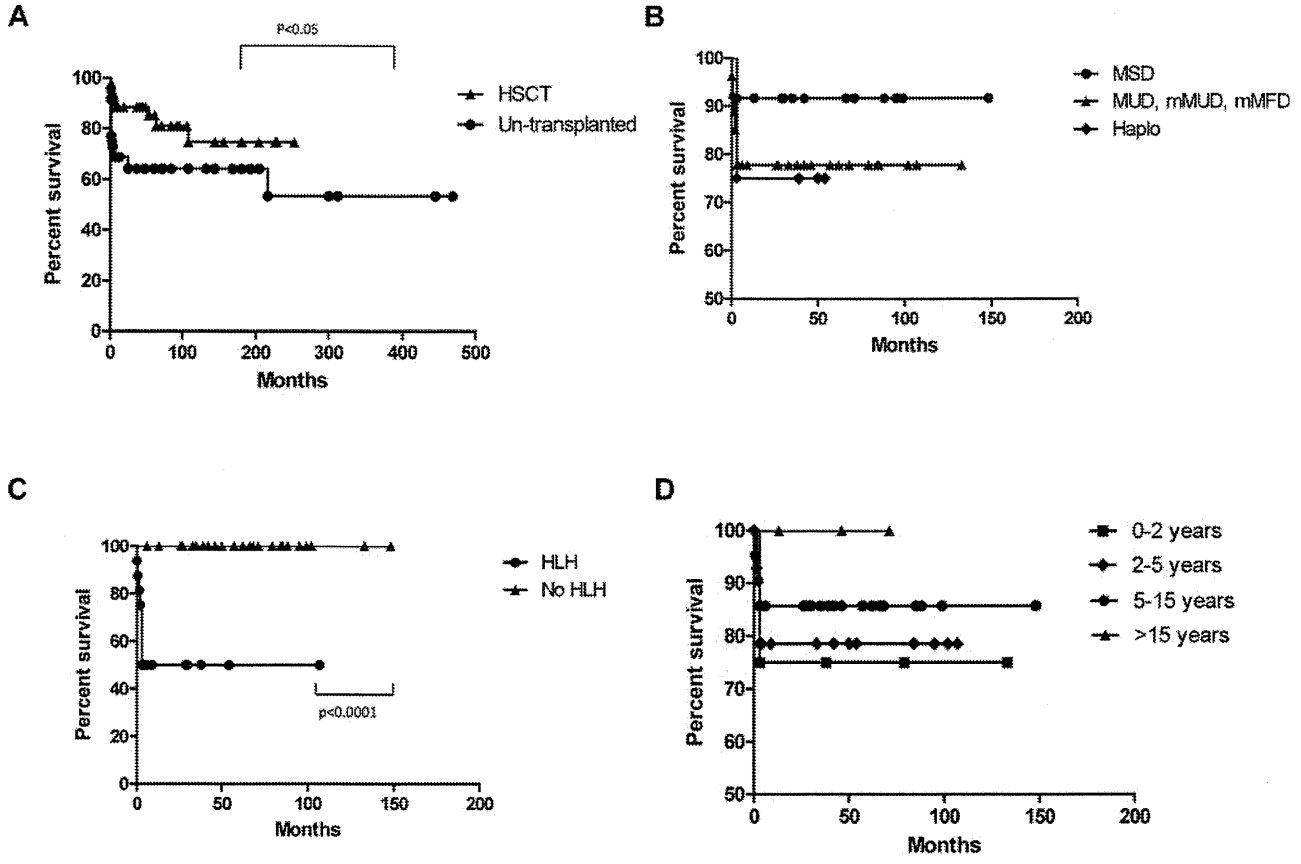

Figure 2. Survival in XLP1 related to different variables. (A) Overall survival of transplanted versus untransplanted patients. In the transplanted group this represents time from presentation and not transplant. (B) Survival according to donor source. (C) Survival after HSCT with relation to presence of HLH before transplant. (D) Survival according to age at transplant.

HLH/FIM was the most common feature in this group being seen in 35 patients (68.6%), with lymphoma present in 10 patients (19.6%), and dysgammaglobulinemia in 19 (37.2%). Nine EBV-positive patients had a family history of XLP1, and two others had a family history suggestive of an X-linked immunodeficiency. Of the 18 EBV-positive patients who died, the majority (14/18) died within 2 months of presentation due to disease progression. Three died in the early posttransplant period of infective complications and disease progression, and 1 died during treatment for lymphoma.

Twenty-eight patients were EBV negative at presentation or diagnosis. The median age of presentation for this group was 3 years (range birth to 31 years). Family history of XLP1 was the presenting feature for 12 patients, and a further 7 patients described a family history suggestive of an X-linked immunodeficiency or lymphoma. There was a higher rate of dysgammaglobulinemia (51.8%) in this group. Lymphoma was present in 7 patients. Fewer EBV negative patients presented with HLH/FIM, and this may suggest that at least for this manifestation a viral trigger is important. Information was sought on other viral infectious agents including cytomegalovirus and adenovirus, but data were not available for most patients. Other clinical features included aplastic anemia in 3 patients and vasculitis in 2 patients. The mortality for this EBV negative group was 28.6% (8/28); 3 patients died shortly after presentation before HSCT with central nervous system vasculitis (2) and HLH with enterococcal sepsis (1). One patient died 11 years after presentation following a complex course, and a further 4 patients died in the early posttransplant period (described in Table 5).

Table 2. Characteristics of EBV-positive and EBV-negative XLP1 patients

	EBV positive (64.6%, n = 51)	EBV negative (35.4%, n = 28)
Median age at presentation	4 y (8 mo-40 y)	3 y (0-31 y)
Family history of XLP1	17.6%	42.9%
HLH	51%	21.4%
FIM	17.6%	
Lymphoma	19.6%	25%
Dysgammaglobulinemia	37.2%	51.8%
Mortality	35.2%	28.6%
Median age at death	3 y 6 mo (14 mo-21 y)	5 y 11 mo (20 mo-31 y)

HSCT for XLP1

HSCT was undertaken in 22 centers (range of patients/center: 1-7) between 1997 and 2009 (Table 3). Forty-six transplants were performed on 43 patients, and the median age at transplant was 6.25 years (range 8 months to 19 years); 1 patient who had undergone a haploidentical transplant received a $CD34^+$ selected boost 1 year after initial transplant. One patient received an allogeneic HSCT to treat lymphoma before a diagnosis of XLP1 was established. Most patients received bone marrow or peripheral blood stem cells, and only 2 patients received umbilical cord HSCT. Donor grafts were from human leukocyte antigen-matched family donors in 14 cases, mismatched family donors or matched unrelated grafts in 28 cases, and haploidentical donors in 4 cases. Half of the transplant procedures (23/46) were performed using myeloablative conditioning regimes including combinations of

Table 3. Characteristics of XLP1 patients receiving allogeneic HSCT

	Percentage	Number	1-y survival	HR	95% CI	*P*
XLP1 features						
Previous HLH	37.2%	16/43	50%	23.93	5.31-108.0	< .0001
Previous NHL	27.9%	12/43	74.2%	0.23	0.05-1.06	.06
Previous dysgammaglobulinemia	46.5%	20/43	80%	1.2	0.29-4.96	.77
EBV+	51.2%	21/41	75%	1.37	0.36-5.3	.65
Age at HSCT	Mean 7 y (8 mo to 19 y 7 mo)					
0-2 y	9.3%	4/43	75%	5.75	0.11-302.1	.38
2-5 y	34.9%	15/43	78.6%	3.61	0.18-71.76	.40
5-15 y	48.8%	21/43	85.7%	3.16	0.11-90.83	.50
> 15 y	7%	3/43	100%			
Year of HSCT						
< 2000	7.0%	3/43	66.7%			
2000-2005	37.2%	16/43	87.5%			
2005-2009	55.8%	24/43	79.2%			
Donor Type						
MSD, MFD	30.4%	14/46	91.77%			
MUD, mMFD, mMUD	60.9%	28/46	77.8%	0.42	0.08-2.07	.27
Haplo	8.7%	4/46	75%	0.24	0.01-6.58	.4
Source						
Bone marrow	58.5%	24/41*	82.6%			
Peripheral blood	36.6%	15/41*	92.9%			
Umbilical cord	4.9%	2/41*	50%			
Conditioning						
MA	50%	23/46	82.9%			
NMA	50%	23/46	78.9%	1.25	0.30-5.2	.77
Serotherapy	30.4%	14/46				
GVHD	50%	19/38				
Grade 1	18.4%	7/38				
Grade 2-3	26.3%	10/38				
Grade 4	5.3%	2/38				
Chronic	5.3%	2/38				
Chimerism						
Full (> 98%)	92%	35/38	100%			
Mixed	8%	3/38	88.8%	2.98	0.06-151.0	.59
Replacement IVIg	20%	7/35†				
Alive	81.4%	35/43				
Follow up	6 wk to 148 mo					

*Data missing on 5 transplants, 1 died during conditioning.

†Three patients < 1 year after transplant.

CI indicates confidence interval; HR, hazard ratio; MSD, matched sibling donor; MFD, matched family donor; MUD, matched unrelated donor; mMFD, mismatched family donor; mMUD, mismatched unrelated donor; Haplo, haploidentical transplant; MA, myeloablative; and NMA, nonmyeloablative.

busulfan 12-20 mg/kg, cyclophosphamide 50-200 mg/kg, and total body irradiation 5-12 Gy. The other half of procedures used nonmyeloablative conditioning regimes consisting of fludarabine (30 mg/kg), melphalan (70-140 mg/kg), busulphan (4-12 mg/kg), or total body irradiation (3-5 Gy). Twenty-six patients received additional serotherapy with alemtuzumab, anti-thymocyte globulin, anti-CD3 antibody, and anti-CD20 antibody (rituximab). Graft-versus-host disease (GVHD) prophylaxis regimes differed between centers, but mostly involved combinations of cyclosporin with methotrexate, mycophenolate mofetil, steroids, and tacrolimus. T-cell depletion of the graft was used in 1 case.

Outcome for XLP1 patients who received allogeneic HSCT was good with 81.4% surviving the procedure (35/43) with a median follow up of 52 months. The majority of these patients (28/35 survivors) required no ongoing immunoglobulin replacement therapy. Tables 3 and 4 highlight details of transplanted patients, and Figure 2 describes survival according to several factors.

Sixteen patients were diagnosed with HLH before transplant and 12 patients had some form of lymphoproliferative disease (lymphoma). Only 51.2% of the cohort had documented evidence of EBV infection (by polymerase chain reaction) with survival rates in EBV+ patients similar to those without EBV infection (75% vs 80%). Most patients experienced some delay from first symptoms to diagnosis (average delay 2 years 7 months) but once a diagnosis of XLP1 was established time to transplant was generally less than 1 year. Median age at transplant was 6.25 years with a range of 8 months to 19 years.

Univariate analysis was performed to identify the major risk factors for survival after HSCT. The most important risk factor was prior HLH, which significantly decreased the survival outcome to 50%. A previous diagnosis of lymphoma had a near significant effect, but other variables were not shown to have a significant effect including importantly, previous evidence of EBV infection, the age at transplant, donor type, or the conditioning regime. It is also important to note that only patients who had HLH at some point before or during transplant died. Conversely, all patients without HLH (n = 27) survived the transplant procedure.

Half of the patients underwent a nonmyeloablative conditioning regime before HSCT and this did not impact on survival (nonmyeloablative vs myeloablative, 78.9% vs 82.9%) or long-term chimerism. More than 90% of patients achieved full donor chimerism, and

Table 4. Details of XLP1 patients surviving allogeneic HSCT

Year of HSCT	EBV	HLH	Age at HSCT	Donor	Conditioning/serotherapy/ graft manipulation	GVHD prophylaxis	GVHD	Chimerism	Follow up (mo)	Ig
1997	NK		7 y	MSD	Cy, TBI	MTX, CSA	1 S*	100%	148	
1998			1 y	MUD	Bu, Cy, ATG	MTX, CSA, P	1 S	100%	133	
2000	+		4 y	MUD	Bu, Cy, Campath	CSA	2 S	100%	102	
2000	+	Yes	3 y	mMUD	Bu, Cy	MTX, CSA	2 S, L	100%	107	
2001			4 y	MUD	Flu, Melph, ATG, TBI	MMF, CSA		100%	102	
2001	+		10 y	MSD	Bu, Cy, VP-16 (NHL)	MTX, CSA	2-3 GI	100%	99	
2001			4 y	MSD	Bu, Cy	CSA	2 S	100%	95	
2002			13 y	MSD	Thio, Flu, ATG	CSA		100%	88	
2002	+		7 y	MUD	Bu, Cy, ATG	MTX, CSA	1 S	100%	85	
2002			3 y	MUD	Bu, Cy, ATG	MTX, CSA		100%	84	
2003			8 mo	mMUD	Flu, Melph, ATG, TBI	TAC, MTX, P	S	100%	79	
2003			19 y	MSD	Thio, Flu, ATG	CSA		100%	71	
2003			11 y	mMUD	Flu, Melph, ATG	MMF, CSA		100%	68	
2004	+		5 y	MSD	Bu, Cy	MTX, CSA		20% PBMC	66	
2004	+		12 y	mMFD	Flu, Melph, Campath, 34^+	MMF, CSA	4 S, L*	100%	62	Y
2004	+		8 y	mMUD	Flu, Melph, Campath	CSA	2-3 S, GI	100%	57	
2005	+	Yes	2 y	Haplo	Bu, Cy, ATG, 34^+	CSA		100%	54	Y
2005			2 y	Haplo	Bu, Cy, ATG, 34^+, top up 1 year	CSA		88% PBMC 97% M	50	Y
2005			12 y	mMUD	Flu, Melph, Campath, 34^+	MMF, CSA	3 S	100%	46	
2005			18 y	MUD		NK		NK	46	NK
2006			5 y	MSD	Bu, Cy	CSA	1 G, 3 S	100%	42	
2006	NK		2 y	MUD	Bu, Flu, Campath	MTX		100%	42	
2006	+		7 y	Haplo	Flu, Melph, Thio, OKT3, ATG			100%, 75% CD3	39	
2006	+	Yes	1 y	MUD	Flu, Melph, Ritux	CSA	1 S	5%	38	
2006	+		11 y	MSD	Bu, Cy, ATG	MTX, CSA		100%	35	
2006			4 y	MUD	Bu, Cy, Campath	MMF, CSA	1 S	100%	33	
2007	+	Yes	6 y	MSD	Bu, Cy	MTX, CSA		99%	30	
2007	+	Yes	7 y	MSD	Bu, Cy	CSA	3 S, L, GI	100%	29	
2007	NK		7 y	MUD	Flu, Melph, TBI	TAC, MTX		98%	27	
2007			7 y	MSD/mMUD	Bu, Cy	CSA	2 S, GI	100%	26	
2008			17 y	MFD	Flu, Melp, Campath	MMF, CSA		100%	13	
2008		Yes	3 y	MUD	Bu, Flu	TAC, MTX		100%	9	Y
2009	+		7 y	MUD	Bu, Cy			100%	6	Y
2009	+	Yes	6 y	mMUD	Flu, Melph, Campath	CSA, MMF	1 S	100%	5	Y
2009	+	Yes	3 y	MUD	Thio, Cy, ATG	CSA, P		100%	4	Y

*Chronic GVHD.

PBMC indicates peripheral blood mononuclear cell; Flu, fludarabine; Melph, melphalan; 34^+, $CD34^+$ stem cell infusion; Bu, busulfan; Cy, cyclophosphamide; Thio, thiotepa; TBI, total body irradiation; CSA, cyclosporin A; MMF, mycophenalate mofetil; MTX, methotrexate; P, prednisolone; TAC, tacrolimus; S, skin; GI, gastrointestinal; L, lung; and Ig, replacement immunoglobulin.

those with a mixed or falling chimerism remained well with 1 patient still receiving replacement immunoglobulin.

Data were also collected on common posttransplant complications such as GVHD, infectious complications and toxicity attributable to chemotherapy. Half of the patients (50%) suffered from some form of GVHD; the majority of cases were grade 1-3 affecting the skin, liver, and gut. Two patients suffered grade 4 disease (of skin and liver), and 1 of these children died. Only 2 patients went on to develop chronic GVHD (see Table 3). One patient experienced both veno-occlusive disease and renal toxicity due to conditioning (busulfan, cyclophosphamide, and antithymocyte globulin), and this patient succumbed shortly after a haploidentical transplant.

In 3 patients with mixed chimerism in peripheral blood mononuclear cells, this remained stable in all but 1 patient, in whom it fell from 92% to 5%. However, this patient remains well 3 years posttransplant and does not require replacement immunoglobulin therapy. From this series, there is little evidence of viral reactivation posttransplant. Thirty-five patients are alive with 5 suffering some long-term effects including EBV viremia (managed with rituximab), bronchiectasis, autoimmune disease, chronic psoriasis, and neutropenia.

Eight patients did not survive after HSCT (see Table 5). Seven patients who died presented with HLH before HSCT (4/7 EBV^+) compared with 8 of 35 survivors, but HLH was a feature of disease in all 8 nonsurvivors. The majority of nonsurvivors were $\leq$ 3 years old (5/8), and conditioning regime did not appear to play a role as 5/8 patients received a full myeloablative regime. The main cause of death in this group was sepsis, but disease progression accounted for 2 deaths. The 2 children dying with disease progression went into transplant with active disease; 1 died during conditioning and the other 3 days after HSCT. One further patient died 3 weeks after HSCT (7 months after presentation) from veno-occlusive disease (VOD), multiorgan failure, and renal toxicity attributable to chemotherapy. The remaining 5 patients died of sepsis (2 pseudomonal sepsis, 1 parainfluenza III infection, 1 with disseminated adenoviral infection, and 1 with EBV and fungal infection) within 3 months of HSCT.

Untransplanted patients

Data were available for 48 patients who did not receive HSCT (Table 6); 30 are alive, 4 of whom are actively awaiting transplant, and 3 who refused HSCT. One patient had received an autologous HSCT before diagnosis with XLP1, and this patient's data were

Table 5. Details of XLP1 patients not surviving allogeneic HSCT

EBV	HLH	Age at HSCT, y	Year of HSCT	Donor	Conditioning/serotherapy/ graft manipulation	GVHD prophylaxis	GVHD	Chimerism	Cause of death
+	Yes	2	2005	MMFD	Flu, TBI	N/A			Died during conditioning 6 wk from presentation
+	Yes	3	2003	MUD	Bu, Flu, Campath, Rituximab	CSA			Died 3 d after HSCT disease progression
	Yes	6	2005	MMFD	Bu, TBI	MMF. MTX, P			Died 14 d after HSCT MDR pseudomonal sepsis
+	Yes	3	2009	Haplo	Bu, Cy, ATG	TCD			Died 3 wk after HSCT VOD, MOF, renal toxicity
+ (after HSCT)	Yes	5	2008	mMUD (cord plus PBSC 4 months later)	Bu, Flu, ATG then Flu, TBI	TAC, P		100%	Died 2 mo after second HSCT EBV, fungal, and ?PCP sepsis
	Yes	3	1998	MSD × 2	Flu, Melph	CSA, P		100%	Died 3 mo after HSCT *Pseudomonas* sepsis
+	Yes	12	2003	MUD	Bu, Cy, Flu, Campath		4 S	100%	Died 3 mo after HSCT disseminated adenovirus
	Yes	1	2007	MUD	Flu, Melph, ATG, 34^+	CSA	2-3 S, L	100%	Died 3 mo after HSCT paraflu III sepsis

PBSC indicates peripheral blood stem cell; Flu, fludarabine; Melph, melphalan; 34^+, $CD34^+$ stem cell infusion; Bu, busulphan; Cy, cyclophosphamide; Thio, thiotepa; TBI, total body irradiation; CSA, cyclosporine A; MMF, mycophenalate mofetil; MTX, methotrexate; P, prednisolone; TAC, tacrolimus; TCD, T-cell depletion; S, skin; L, lung; VOD, veno-occlusive disease; MOF, mullti-organ failure; MDR, multidrug resistant; and PCP, *Pneumocystis jiroveci*.

analyzed as though untransplanted. Less detailed information was available for this set of patients compared with those receiving HSCT. This may be because some patients died before EBV status and immune function could be established and any first symptoms may not have been recognized as a manifestation of XLP1. From data available, median age at presentation was 5 years, and delay in diagnosis ranged from a few weeks to 32 years.

Presentation was highly variable but as expected included HLH/FIM, dysgammaglobulinemia, and recurrent infection. More unusual presentations included 1 patient with central nervous system vasculitis, intracranial hemorrhage and myocardial fibrosis, and peripheral eosinophilia. The course of XLP1, both temporal and clinical, was extremely variable without any apparent correlation to family history or genetic mutation.

Table 6. Characteristics of XLP1 patients not receiving HSCT

		Number
Age at first symptom	8 y 8 mo (6 mo-40 y)	
Age at death	7.5 y (1-31 y)	
Time from presentation to death	17.3 mo (1 NK) 9 d-18 y	
Time from first symptom (in those patients alive)	12 y (1 NK) 1-39 y	
Presenting symptom		
HLH	31.3%	15/48
FIM	10.4%	5/48
Lymphoma	16.7%	8/48
Dysgammaglobulinemia	29.2%	14/48
Other	12.5%	6/48
Features		
HLH	33.3%	16/48
FIM	12.5%	6/48
Lymphoma	20.1%	10/48
Dysgammaglobulinemia	56.3%	27/48
Gut	8.3%	4/48
Other	14.6%	7/48
EBV status		
EBV^+	66.6%	32/48
EBV^-	14.6%	7/48
Unknown	18.8%	9/48
Mortality	37.5%	18/48 (4 EBV^-)
Associated with HLH	81.3%	13/16
Associated with FIM	33.3%	2/6
Associated with lymphoma	20%	2/10 1 had previous HLH and died during chemotherapy; 1 had recurrent lymphoma and many other problems
Immunoglobulin replacement		
Yes	70%	21/30
No	23.3%	7/30
Unknown	6.7%	2/30

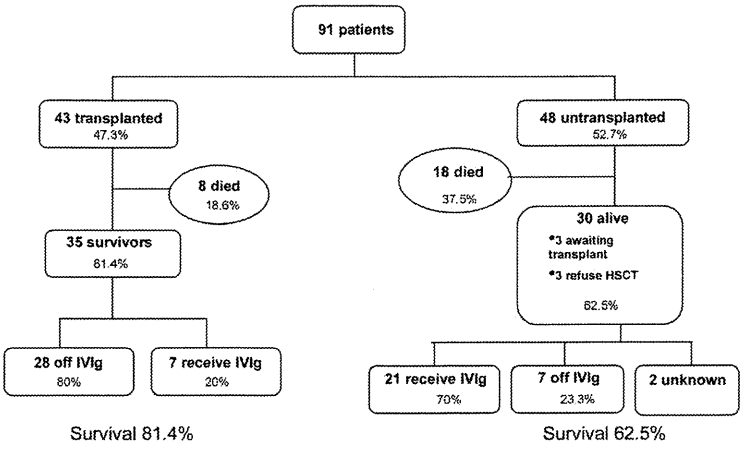

Figure 3. Outcome of patients with SAP/*SH2D1A* mutations.

As with transplanted patients the significant mortality associated with HLH is evident in untransplanted patients (81.3%). Presentation or manifestation of HLH (n = 15 and 16, respectively) was associated with a rapid decline and death within 6 weeks, especially in patients less than 5 years of age. Of the 48 patients, 32 did not have manifestations of HLH, and in this group 5 died, thereby giving a survival of 84.4% with a mean follow-up in this group of 11.6 years. For those untransplanted patients who survive, 70% received replacement immunoglobulin therapy, with few suffering from long-term complications. Only 5 patients have recorded complications, including 1 with recurrent infection, 1 with neutropenia, 1 with bronchiectasis, and 2 boys with gastrointestinal disease and growth delay.

Supplemental Table 2 compares the demographics between transplanted and untransplanted patients. No significant differences were seen between the 2 populations other than mortality, which was twice as high in the untransplanted cohort ($P < .05$). Age of death was lower in transplanted patients and may reflect the more severe course that may have led to the need for HSCT.

Discussion

This report summarizes data on 91 patients from 64 families worldwide with a genetic diagnosis of XLP1 and provides information on outcome with and without allogeneic HSCT using current treatment protocols (summarized in Figure 3). This report is the first large-scale analysis of XLP1 patients since the report by the XLP1 registry in 1995 and has for the first time gathered patients who have confirmed SAP/*SH2D1A* mutations. Therefore this report represents a genetically homogeneous cohort and avoids possible phenotypic variability through inclusion of other patients with genetic defects such as *XIAP/BIRC* 4 mutations.

The clinical features of the disease are similar to those reported by the XLP1 Registry, with HLH and FIM remaining the most common and most lethal complication. With the advent of more accessible genetic screening and mutation analysis confirming the diagnosis, more patients have been diagnosed early on the basis of family history and increased awareness of the disease has also led to patients being diagnosed after presentation with immune dysregulation and more unusual presenting features such as vasculitis.

A diagnosis of XLP1 is still a difficult one to make, and it is possible that some patients mistakenly fall under the umbrella of common variable immunodeficiency, although previous genetic screening studies suggest that the incidence of XLP1 patients in common variable immunodeficiency cohorts is low.[33] It is also possible that there are older individuals who present in adulthood and have not been identified and included in this study, and this may result in a bias in the method of data collection as the majority of centers approached to contribute data were specialist pediatric centers. For example, a recent case report describes a 41-year-old man who presented with an EBV-induced central nervous system B-cell lymphoma and absent B cells.[34] The oldest surviving patient from this cohort presented at the age of 7 years with recurrent infections and hypogammaglobulinemia, but remains well without transplant and is receiving replacement immunoglobulin therapy at 46 years of age.

The prognosis for XLP1 has greatly improved since 1995, when Seemayer et al[2] reported an overall survival of 25% survival with 71.4% of patients in this cohort alive at the time of data analysis. Indeed, the mortality in untransplanted patients was lower than we expected, with 62.5% surviving, including 3 boys who presented with HLH, but the mortality in this group secondary to HLH remains high at 81.3%. It is also interesting to note that a considerable mortality of 28.6% is seen in EBV-negative patients who do not receive HSCT and is related to HLH, sepsis, and vasculitis, suggesting that underlying immunological abnormalities in XLP1, and not only EBV-driven disease, can be fatal. Few complications from recurrent infection and immune dysregulation were reported, suggesting that early diagnosis and good supportive care with replacement immunoglobulin and prophylactic antibiotics can improve the outcome for untransplanted patients. Although over 60% of patients survive without HSCT, it will be important to follow patients carefully, since there is the potential for more severe manifestations to arise, and the options for transplant should be explored.

The mortality associated with the different clinical phenotypes has changed over time, with an improved survival for both HLH (34.5% vs 4%) and lymphoma (91% vs 35%).[2] This most likely reflects improved treatment strategies for both HLH (especially the use of agreed protocols such as HLH 94[35] and 2004[36]) and malignancy. Although these figures represent survival with either HLH or lymphoma as features of XLP1 at any stage, they are very similar to the survival seen if patients present with these features (44.5% and 92% for HLH/FIM and lymphoma, respectively). A mortality of 13% in patients who exhibit dysgammaglobulinemia is associated with HLH, infection, vasculitis, and hemorrhage and highlights that although clinically this phenotype may be milder, it is not an innocuous phenotype, and progression to further fatal symptoms is not uncommon.

The outcome data following allogeneic HSCT from this report is encouraging. The outcome data presented is the largest ever

gathered and shows that approximately 80% of patients survive the procedure with complete cellular and humoral reconstitution in the large majority of cases. In this series, there is little evidence of problematic EBV reactivation adversely affecting transplant outcome and no increased incidence of long-term complicating features such as autoimmunity in comparison to transplant for other conditions.[37,38] Although donor chimerism in the majority of patients was complete, even low level chimerism in 2 patients with 5% and 20% donor chimerism was associated with good immune recovery. Conversely however, when the patients who required ongoing immunoglobulin support are analyzed, all but 1 have 100% donor engraftment. Further detailed lineage-specific analysis and study of T- and B-cell function in these patients is necessary to determine why humoral function has not been established. The availability of a fully matched donor is associated with an improved survival outcome (approximately 92%), although with the present low numbers this is not statistically significant. Haploidentical grafts show a good outcome in this cohort, but the numbers are extremely low (only 4 transplants performed), and therefore this information needs to be interpreted with caution.

The most important factor affecting survival after transplant is a manifestation of HLH, which significantly reduces survival to 50%. Indeed all 8 patients who died had a complication of HLH at some point in their clinical course. This may reflect the effects of HLH itself or HLH chemotherapy and immunosuppression on the transplant process, including increased organ related toxicity and increased susceptibility to pathogens. In comparison to data reported on cohorts of patients undergoing transplant for HLH associated with other gene defects (eg, perforin and munc 13-4)[39-41] it appears that the outcome for HLH associated with XLP1 is worse and may relate to the multiple immune deficits associated with SAP deficiency. By contrast all XLP1 patients who had no HLH manifestations (n = 27) survived the HSCT procedure.

These data may now allow more informed recommendations to be made regarding transplantation in XLP1. It is clear from this report that HLH in XLP1 has a very poor prognosis if left untransplanted. Therefore any individual with HLH as a manifestation of XLP1 should undergo allogeneic HSCT.

For patients who are newly diagnosed because of a family history but with no clinical features or for those who present with manifestations other than HLH/FIM, the decision to transplant a relatively well child has been more challenging. An important observation from this report is that all patients (n = 27) who went into transplant without prior HLH survived the procedure in comparison to 84.4% survival for those who are untransplanted and have not manifested with HLH. Since progression to HLH without transplant may occur at a later stage, there is a strong argument to transplant all individuals with a diagnosis of XLP1.

However, there is a counter argument to such a recommendation. As with other immunodeficiencies, the data collected and presented here may not give a complete picture of the natural course of XLP1 and is a historical cohort study conducted before the advent of recent improved therapies. Further, milder patients may also remain undiagnosed having been labeled with a diagnosis of common variable immunodeficiency. It is also the case that HLH is most often seen in younger patients (median age of presentation 3.2 years) and older individuals are less likely to manifest with HLH. There may also be reluctance on the part of families and physicians to undertake a transplant in a well child given that, even in the best-case scenario, there will be a certain mortality associated with any allogeneic transplant procedure.

A more pragmatic recommendation would be to undertake transplant in all patients presenting or manifesting with HLH. Similarly for newly diagnosed or young children without any HLH, if a well-matched donor is available, HSCT should be undertaken, since a manifestation of HLH may be catastrophic or may severely compromise transplant outcome. For older individuals, we would still recommend that HSCT be undertaken, but this decision to transplant should be based on available donor status, wellbeing of the patient, and the attitude of family and physician to the risk of transplant. If HSCT is not undertaken immediately, it is recommended that a donor source is identified and that all patients are followed very carefully in case of disease progression and onset of other manifestations, at which point HSCT could be performed rapidly.

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Authorship

Contribution: C.B. designed the research, collected and acquired data, analyzed the data, and wrote the manuscript; H.B.G. assumed overall responsibility for the research, oversaw analysis, and revised the manuscript; and all authors contributed clinical data and reviewed the manuscript before submission.

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References

1. Purtilo DT, Cassel CK, Yang JP, Harper R. X-linked recessive progressive combined variable immunodeficiency (Duncan's disease). *Lancet.* 1975;1(7913):935-940.
2. Seemayer TA, Gross TG, Egeler RM, et al. X-linked lymphoproliferative disease: twenty-five years after the discovery. *Pediatr Res.* 1995;38(4):471-478.
3. Purtilo DT, Grierson HL. Methods of detection of new families with X-linked lymphoproliferative disease. *Cancer Genet Cytogenet.* 1991;51(2):143-153.
4. Sumegi J, Huang D, Lanyi A, et al. Correlation of mutations of the SH2D1A gene and Epstein-Barr virus infection with clinical phenotype and outcome in X-linked lymphoproliferative disease. *Blood.* 2000;96(9):3118-3125.
5. Rougemont AL, Fournet JC, Martin SR, et al. Chronic active gastritis in X-linked lymphoproliferative disease. *Am J Surg Pathol.* 2008;32(2):323-328.
6. Talaat KR, Rothman JA, Cohen JI, et al. Lymphocytic vasculitis involving the central nervous system occurs in patients with X-linked lymphoproliferative disease in the absence of Epstein-Barr virus infection. *Pediatr Blood Cancer.* 2009;53(6):1120-1123.
7. Loeffel S, Chang CH, Heyn R, et al. Necrotizing lymphoid vasculitis in X-linked lymphoproliferative syndrome. *Arch Pathol Lab Med.* 1985;109(6):546-550.
8. Kanegane H, Ito Y, Ohshima K, et al. X-linked lymphoproliferative syndrome presenting with systemic lymphocytic vasculitis. *Am J Hematol.* 2005;78(2):130-133.

9. Sayos J, Wu C, Morra M, et al. The X-linked lymphoproliferative-disease gene product SAP regulates signals induced through the co-receptor SLAM. *Nature.* 1998;395(6701):462-469.
10. Coffey AJ, Brooksbank RA, Brandau O, et al. Host response to EBV infection in X-linked lymphoproliferative disease results from mutations in an SH2-domain encoding gene. *Nat Genet.* 1998; 20(2):129-135.
11. Nichols KE, Harkin DP, Levitz S, et al. Inactivating mutations in an SH2 domain-encoding gene in X-linked lymphoproliferative syndrome. *Proc Natl Acad Sci U S A.* 1998;95(23):13765-13770.
12. Okano M, Gross TG. Epstein-Barr virus-associated hemophagocytic syndrome and fatal infectious mononucleosis. *Am J Hematol.* 1996; 53(2):111-115.
13. Dupre L, Andolfi G, Tangye SG, et al. SAP controls the cytolytic activity of CD8+ T cells against EBV-infected cells. *Blood.* 2005;105(11):4383-4389.
14. Sharifi R, Sinclair JC, Gilmour KC, et al. SAP mediates specific cytotoxic T-cell functions in X-linked lymphoproliferative disease. *Blood.* 2004;103(10):3821-3827.
15. Benoit L, Wang X, Pabst HF, Dutz J, Tan R. Defective NK cell activation in X-linked lymphoproliferative disease. *J Immunol.* 2000;165(7): 3549-3553.
16. Nakajima H, Cella M, Bouchon A, et al. Patients with X-linked lymphoproliferative disease have a defect in 2B4 receptor-mediated NK cell cytotoxicity. *Eur J Immunol.* 2000;30(11):3309-3318.
17. Tangye SG, Phillips JH, Lanier LL, Nichols KE. Functional requirement for SAP in 2B4-mediated activation of human natural killer cells as revealed by the X-linked lymphoproliferative syndrome. *J Immunol.* 2000;165(6):2932-2936.
18. Bottino C, Augugliaro R, Castriconi R, et al. Analysis of the molecular mechanism involved in 2B4-mediated NK cell activation: evidence that human 2B4 is physically and functionally associated with the linker for activation of T cells. *Eur J Immunol.* 2000;30(12):3718-3722.
19. Nichols KE, Hom J, Gong SY, et al. Regulation of NKT cell development by SAP, the protein defective in XLP. *Nat Med.* 2005;11(3):340-345.
20. Chung B, Aoukaty A, Dutz J, Terhorst C, Tan R. Signaling lymphocytic activation molecule-associated protein controls NKT cell functions. *J Immunol.* 2005;174(6):3153-3157.
21. Ma CS, Pittaluga S, Avery DT, et al. Selective generation of functional somatically mutated IgM+CD27+, but not Ig isotype-switched, memory B cells in X-linked lymphoproliferative disease. *J Clin Invest.* 2006;116(2):322-333.
22. Nichols KE, Ma CS, Cannons JL, Schwartzberg PL, Tangye SG. Molecular and cellular pathogenesis of X-linked lymphoproliferative disease. *Immunol Rev.* 2005;203:180-199.
23. Ma CS, Hare NJ, Nichols KE, et al. Impaired humoral immunity in X-linked lymphoproliferative disease is associated with defective IL-10 production by CD4+ T cells. *J Clin Invest.* 2005; 115(4):1049-1059.
24. Gilmour KC, Cranston T, Jones A, et al. Diagnosis of X-linked lymphoproliferative disease by analysis of SLAM-associated protein expression. *Eur J Immunol.* 2000;30(6):1691-1697.
25. Okano M, Pirruccello SJ, Grierson HL, et al. Immunovirological studies of fatal infectious mononucleosis in a patient with X-linked lymphoproliferative syndrome treated with intravenous immunoglobulin and interferon-α. *Clin Immunol Immunopathol.* 1990;54(3):410-418.
26. Trottestam H, Beutel K, Meeths M, et al. Treatment of the X-linked lymphoproliferative, Griscelli and Chediak-Higashi syndromes by HLH directed therapy. *Pediatr Blood Cancer.* 2009;52(2):268-272.
27. Lankester AC, Visser LF, Hartwig NG, et al. Allogeneic stem cell transplantation in X-linked lymphoproliferative disease: two cases in one family and review of the literature. *Bone Marrow Transplant.* 2005;36(2):99-105.
28. Strahm B, Rittweiler K, Duffner U, et al. Recurrent B-cell non-Hodgkin's lymphoma in two brothers with X-linked lymphoproliferative disease without evidence for Epstein-Barr virus infection. *Br J Haematol.* 2000;108(2):377-382.
29. Arkwright PD, Makin G, Will AM, et al. X linked lymphoproliferative disease in a United Kingdom family. *Arch Dis Child.* 1998;79(1):52-55.
30. Amrolia P, Gaspar HB, Hassan A, et al. Non-myeloablative stem cell transplantation for congenital immunodeficiencies. *Blood.* 2000;96(4): 1239-1246.
31. Hugle B, Suchowerskyj P, Hellebrand H, et al. Persistent hypogammaglobulinemia following mononucleosis in boys is highly suggestive of X-linked lymphoproliferative disease - report of three cases. *J. Clin Immunol.* 2004;24(5):515-522.
32. Nistala K, Gilmour KC, Cranston T, et al. X-linked lymphoproliferative disease: three atypical cases. *Clin Exp Immunol.* 2001;126(1):126-130.
33. Eastwood D, Gilmour KC, Nistala K, et al. Prevalence of SAP gene defects in male patients diagnosed with common variable immunodeficiency. *Clin Exp Immunol.* 2004;137(3):584-588.
34. Hervier B, Latour S, Loussouarn D, et al. An atypical case of X-linked lymphoproliferative disease revealed as a late cerebral lymphoma. *J Neuroimmunol.* 2009;218(1-2):125-128.
35. Henter JI, Arico 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(5):342-347.
36. Henter JI, Horne A, Arico M, et al. HLH-2004: diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis. *Pediatr Blood Cancer.* 2007;48(2):124-131.
37. O'Brien TA, Eastlund T, Peters C, et al. Autoimmune haemolytic anaemia complicating haematopoietic cell transplantation in paediatric patients: high incidence and significant mortality in unrelated donor transplants for non-malignant diseases. *Br J Haematol.* 2004;127(1):67-75.
38. Sonici E, Bennato B, Bertoni E, et al. Autoimmunity after BMT in primary immunodeficiency diseases: single centre report of 184 children [abstract]. 36th Annual Meeting of the European Group for Blood and Marrow Transplantation; 2010.
39. Cooper N, Rao K, Gilmour K, et al. Stem cell transplantation with reduced-intensity conditioning for hemophagocytic lymphohistiocytosis. *Blood.* 2006;107(3):1233-1236.
40. Yoon HS, Im HJ, Moon HN, et al. The outcome of hematopoietic stem cell transplantation in Korean children with hemophagocytic lymphohistiocytosis. *Pediatr Transplant.* 2010;20(2):438-45.
41. Ohga S, Kudo K, Ishii E, et al. Hematopoietic stem cell transplantation for familial hemophagocytic lymphohistiocytosis and Epstein-Barr virus-associated hemophagocytic lymphohistiocytosis in Japan. *Pediatr Blood Cancer.* 2010;54(2):299-306.

Clinical similarities and differences of patients with X-linked lymphoproliferative syndrome type 1 (XLP-1/SAP deficiency) versus type 2 (XLP-2/XIAP deficiency)

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X-linked lymphoproliferative syndromes (XLP) are primary immunodeficiencies characterized by a particular vulnerability toward Epstein-Barr virus infection, frequently resulting in hemophagocytic lymphohistiocytosis (HLH). XLP type 1 (XLP-1) is caused by mutations in the gene *SH2D1A* (also named *SAP*), whereas mutations in the gene *XIAP* underlie XLP type 2 (XLP-2). Here, a comparison of the clinical phenotypes associated with XLP-1 and XLP-2 was performed in cohorts of 33 and 30 patients, respectively. HLH (XLP-1, 55%; XLP-2, 76%) and hypogammaglobulinemia (XLP-1, 67%; XLP-2, 33%) occurred in both groups. Epstein-Barr virus infection in XLP-1 and XLP-2 was the common trigger of HLH (XLP-1, 92%; XLP-2, 83%). Survival rates and mean ages at the first HLH episode did not differ for both groups, but HLH was more severe with lethal outcome in XLP-1 (XLP-1, 61%; XLP-2, 23%). Although only XLP-1 patients developed lymphomas (30%), XLP-2 patients (17%) had chronic hemorrhagic colitis as documented by histopathology. Recurrent splenomegaly often associated with cytopenia and fever was preferentially observed in XLP-2 (XLP-1, 7%; XLP-2, 87%) and probably represents minimal forms of HLH as documented by histopathology. This first phenotypic comparison of XLP subtypes should help to improve the diagnosis and the care of patients with XLP conditions. (*Blood*. 2011;117(5):1522-1529)

Introduction

X-linked lymphoproliferative syndrome (XLP) is a rare immunodeficiency condition characterized by an extreme vulnerability to Epstein-Barr virus (EBV) infection, frequently resulting in hemophagocytic lymphohistiocytosis (HLH) or virus-associated hemophagocytic syndrome (VAHS).[1-3] HLH is caused by overwhelming T-cell and macrophage activation, leading to fever, splenomegaly, cytopenia, hypofibrinogenemia, or hypertriglyceridemia, hyperferritinemia, and hemophagocytosis.[4]

XLP belongs to the group of familial hemophagocytic lymphohistiocytosis (FHL) as originally proposed by Purtilo et al.[1] In the original description, the term "lymphoproliferative disease" in the Duncan kindred[1] was used for benign or malignant lymphoproliferation but also for the diffuse organ "infiltrates composed of lymphocytes, plasma cells, and histiocytes, some containing erythrocytes," describing histologic features of HLH. Thus, the term "X-linked lymphoproliferative disease or syndrome" used thereafter to name this condition refers not only to malignant lymphomas but also to HLH. Two genetic causes are responsible for XLP. XLP type 1 (XLP-1) is caused by hemizygous mutations in the gene *SH2D1A* encoding the signaling lymphocyte activation molecule (SLAM)–associated protein (SAP) (MIM no. 308240).[5,6] Hemizygous mutations in the gene encoding the X-linked inhibitor of

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apoptosis protein (XIAP; also termed *BIRC4*; MIM no. 300635) have been discovered in a cohort of patients with clinical XLP without any identified mutations in *SH2D1A* and normal SAP protein expression.[7] Thus, mutations in *XIAP* define the XLP type 2 (XLP-2). These findings were confirmed by the identification of additional patients with XIAP deficiency.[8,9] After EBV infection in most (but not all) cases, patients bearing mutations in *SH2D1A* (hereafter denoted SAP-deficient patients) may experience variable manifestations such as fulminant infectious mononucleosis corresponding pathophysiologically to HLH, malignant lymphoma, and hypogammaglobulinemia.[2,10,11] Less common findings are dysgammaglobulinemia, bone marrow hypoplasia, especially aplastic anemia, and lymphocytic vasculitis.[12,13] However, although HLH is almost always triggered by EBV, the other manifestations can be present even in SAP-deficient patients who have never encountered EBV.[2,3,10,11] The clinical features of the 12 patients with mutations in *XIAP* (hereafter denoted XIAP-deficient patients) initially described, slightly differed from the features described above. In some XIAP-deficient patients, splenomegaly was noticed as the first clinical symptom, and chronic colitis occurred during the disease course in 2 patients.[7]

The gene product affected in XLP-1 patients, SAP, is a small SH2-containing adaptor protein that is expressed in T, natural killer (NK), and invariant NKT (iNKT) cells.[5,14] SAP binds with high affinity and specificity to tyrosine-based motifs located in the cytoplasmic domains of the transmembrane receptors of the SLAM family. SAP couples SLAM family receptors to downstream signaling pathways and thereby enables SLAM receptors to mediate an array of activating or regulatory signals. In SAP-deficient humans and mice, multiple cellular defects have been documented, including altered $CD8^+$ T- and NK-cell cytotoxicity responses, $CD4^+$ T helper cell cytokine production and function, block of CD1d-restricted iNKT-cell development, defective antibody production associated with reduced numbers of switched memory B cells and defects in germinal center formation.[11,14] Studies of SAP-deficient humans and mice support the notion that the immune dysfunctions seen in SAP-deficiency are mostly caused by alterations in the signal transduction of SLAM family receptors.

The XLP-2 gene product, XIAP, belongs to the family of inhibitor of apoptosis proteins and is well known to be a potent physiologic inhibitor of caspases 3, 7, and 9.[15] XIAP is ubiquitously expressed.[7] In addition to its antiapoptotic role, XIAP is also involved in multiple signaling pathways, including copper metabolism, activation of the nuclear factor κB and the mitogen-activated protein kinases pathways and the transforming growth factor-β–receptor and bone morphogenetic protein–receptor signal transduction.[16] In XIAP-deficient patients, lymphocytes are characterized by an increased susceptibility to apoptosis in response to CD95 and tumor necrosis factor receptor–related apoptosis-inducing ligand receptor stimulation as well as enhanced activation-induced cell death.[7] XIAP-deficient patients also display low but detectable numbers of iNKT cells in blood although a recent study indicated that they can have normal numbers of iNKT cells.[9] NK cell–mediated cytotoxicity is apparently normal in XIAP-deficient patients.[7,9]

Our knowledge of the immune dysfunctions underlying the clinical manifestations in SAP-deficient patients has been largely improved in the past decade. However, this is not the case for XIAP-deficient patients. A better characterization of the clinical similarities and the differences between XLP-1 and XLP-2 could provide hints for a better understanding of the pathogenesis of these conditions and, furthermore, improve diagnostic and therapeutic procedures for these patients. Therefore, we performed a retrospective analysis of the clinical features observed in cohorts of 33 SAP- and 30 XIAP-deficient patients.

Methods

Patients and diagnosis

We performed a retrospective analysis of the clinical and laboratory features of SAP- and XIAP-deficient patients in whom confirmative molecular diagnosis had been performed at the Necker Children's Hospital. Patient conditions were diagnosed as XLP-1 and XLP-2 on the basis of molecular results or on the basis of clinical features when disease had been molecularly proven in male relatives on the mother's side (supplemental Methods and Results, available on the *Blood* Web site; see the Supplemental Materials link at the top of the online article). Patients and families provided informed consent for genetic and immunologic studies in accordance to the 1975 Declaration of Helsinki, and the study was approved by the local ethics regulations (Necker-Enfants Malades Ethical Board Committee).

Protein expression

Expression of SAP and XIAP was analyzed by Western blotting or flow cytometry or both after intracellular staining in phytohemagglutinin-induced T-cell blasts or peripheral blood mononuclear cells or both as described.[7] The monoclonal antibody (mAb) anti-SAP was kindly provided by Dr A. Veillette, IRCM, Montréal. Intracellular SAP was stained by fluorescein isothiocyanate– or phycoerythrin-coupled anti-SAP mAb and XIAP detected with noncoupled anti-XIAP mouse mAb (clone 48; BD Biosciences) revealed with fluorescein isothiocyanate–coupled anti–mouse antibodies (Jackson ImmunoResearch Laboratories Inc) after cell permeabilization with Perm 2 (BD Biosciences).

Histology and immunohistochemistry

All diagnostic specimens were fixed in 10% buffered formalin and stained with hematoxylin and eosin, Giemsa, or trichrome dyes (for the liver). Immunohistochemistry was performed on fixed tissues with a peroxidase-based method (Dako). Antibodies used were raised against CD20, CD3, CD8, and latent membrane protein 1 (LMP-1) (Dako); CD25 (Novocastra); and T-cell intracellular antigen-1 (Immunotech). EVB-encoded RNA (EBER) was probed on some specimen with the use of in situ hybridization technique. Slides were observed using a Leica DM LB microscope with ×20, ×40, and ×100 objectives and a 10× eyepiece. Acquisition of images was with IM50 software (Leica Microsystems). All slides were analyzed by the same pathologist (D.C.), and an independent review was also performed (F.H.).

Clinical assessment

The patients' clinical events and laboratory features were assessed retrospectively by retrieval of data from medical records.

Statistical analysis

The statistical analyses were performed with Fisher exact tests or log-rank tests (for comparison of survival curves) with the use of the PRISM software (GraphPad Software Inc).

Results

XLP-1 was diagnosed in 33 patients from 19 families, and mutations of *SH2D1A* were found in 18 families, and XLP-2 was

Table 1. Characteristics of patients with mutations in *SH2D1A/SAP* (XLP-1)

Patient ID*	*SH2D1A/SAP* mutation	SAP protein	HLH (age in years at diagnosis)	EBV at first HLH	HLH relapses (age in years at relapse)	SM (age in years at diagnosis)	Hypo-γ (age in years at diagnosis)	Lymphoma (age in years at diagnosis)	Other manifestations (age in years at diagnosis)	Outcome (age in years)
S1.1	E67G		–	NA		–	–	13	–	Alive, well (19)
S1.2	E67G	–	3	+	+ (25)	–	+ (26)	34	–	Alive, under lymphoma treatment (34)
S1.3	E67G		15	?	–	–	–	7, 30	–	Alive, under lymphoma treatment (30)
S1.4	E67G		–	NA		–	+ (4)†	–	–	Alive, well, IVIG (10)
S2.1	I96X	–	4	?	–	?	?	–	–	Died (4, HLH)
S3.1	del. of exons 1-4		–	NA		–	+†	–	Chronic gastritis,	Alive, well, IVIG (20)
S3.2	del. of exons 1-4		–	NA		–	+†	–	IM (2), chronic gastritis	Alive, well, IVIG (20)
S4.1	R55X		–	NA		–	–	40	–	Alive, well (42)
S4.2	ND		6	+	–	–	–	–	–	Died (6, HLH)
S5.1	del. of exon 2		3.7	+	–	?	?	–	–	Died (3.7, HLH)
S5.2	ND		–	NA		–	?	5	–	Died (5, lymphoma)
S6.1	del. of exon 1		2.2	+	–	–	?	–	–	Died (2.2, HLH)
S7.1	R55X	–	2.5	+	–	–	?	–	Recurrent infections	HSCT (2.7), alive (11)
S8.1	X129RfsX141	–	2.4	+	+ (9)	–	+ (3)†	–	–	First HSCT (9); second HSCT (10); died (10.2)
S8.2	ND		2	+	–	–	?	–	–	Died (2, HLH)
S9.1	C42Y	+/–	–	NA		–	–	2	–	Alive (18)
S9.2	C42Y		–	NA		–	+ (1)†	–	–	Alive, well, IVIG (16)
S10.1	R55Q		14	?	–	?	?	–	–	Died (14, HLH)
S11.1	X129R fsX141	–	–	NA		–	+	–	–	Alive, well, N+T, IVIG (22)
S11.2	X129R fsX141		–	NA		?	?	–	Recurrent pneumonia	Alive, well (66)
S11.3	X129R fsX141		–	NA		–	+	–	–	Alive, well, IVIG (15)
S11.4	X129R fsX141		–	NA		–	+ (9)	7	–	Alive, well, IVIG (19)
S12.1	del. of exon 3	–	19	+	–	–	+ (10)†	11	T (22)	Alive, T, IVIG (23)
S12.2	del. of exon 3		19	?	–	–	+ (19)†	20	–	Died (21, lymphoma)
S13.1	N82FfsX103	ND	10§	–	+ (12, EBV+)	+ (9)‡	?	–	–	Died (12, HLH)
S14.1	del. of exons 1-4		3.5	+	–	–	–	–	HUS (3.5)	Died (3.6, HLH)
S15.1	A22P	–	–	NA		–	+ (13)†	–	–	Alive, well, IVIG (25)
S15.2	ND		3.6	?	–	–	?	–	–	Died (3.6, HLH)
S15.3	ND		–	NA		+ (45)‡	?	–	–	Died (69, myelodysplasia)
S16.1	del. of exons 2-4	–	3.1	+	–	–	?	–	–	Died (3.1, HLH)
S17.1	M1T	–	–	NA	–	–	+ (4)†	–	IM (2.4)	Alive, N+T, IVIG (20)
S18.1	No mutation	–	16§	?	–	–	+ (15)†	9	–	Died (17, HLH)
S19.1	del. of exons 1-4	–	3.3	+		–	–	–	Hypopigmented hair	HSCT (3.7), died (3.8)

SM indicates recurrent splenomegaly or hepatosplenomegaly; Hypo-γ, hypogammaglobulinemia; NA, not applicable; del., deletion; ?, unknown; IM, infectious mononucleosis; ND, not done; HSCT, hematopoietic stem cell transplantation; N, neutropenia; T, thrombocytopenia; and HUS, hemolytic uremic syndrome.

*Patient identification: S indicates SAP-deficiency, the first number corresponds to the family and the second to the individual patient.

†With recurrent respiratory infections; + indicates yes or positive; –, no or negative.

‡Recurrent splenomegaly or hepatosplenomegaly associated with intermittent fever, anemia, and cytopenia.

§Diagnosed as incomplete HLH.

diagnosed in 30 patients from 11 families (Tables 1 and 2). In one patient (PS18.1), no mutation in *SH2D1A* was found; however, no SAP protein expression was detected.[17] Six and 7 mutations in *SH2D1A* and *XIAP* were novel and not reported, respectively (supplemental Methods and Results).

Clinical manifestations included HLH, splenomegaly and incomplete forms of HLH, lymphoma, dysgammaglobulinemia, colitis, and rare clinical manifestations.

HLH

The mean age at first episode of HLH was 7.35 years (range, 2.0-19.0 years) in SAP-deficient and 6.5 years (range, 0.1-23.0 years) in XIAP-deficient patients ($P = .89$). The occurrence of HLH in SAP-deficient (18 of 33, 55%) and in XIAP-deficient (22 of 29, 76%, one unknown) patients did not differ significantly ($P = .112$) (Figure 1A; Table 3). XIAP-deficient patients with null mutations (families X1 to X7 and X11) more frequently developed HLH (19 of 20, 95%) compared with XIAP-deficient patients expressing non-null mutations (families X8, X9, and X10; 3 of 9, 33%; $^{**}P = .0011$; supplemental Figure 1A).

Overall, 11 of the 33 SAP-deficient patients (33%) and 5 of 30 the XIAP-deficient patients (17%) succumbed to HLH ($P = .1563$). Among patients with HLH, HLH-associated lethality was significantly higher in SAP-deficient patients (11 of 18, 61%) than in XIAP-deficient patients (5 of 22, 23%) ($^{*}P = .0230$). HLH

Table 2. Characteristics of patients with mutations in *XIAP* (XLP-2)

Patient ID*	*XIAP* mutation	XIAP protein	HLH (age in years at diagnosis)	EBV at first HLH	HLH relapses (age in years at relapse)	SM (age in years at diagnosis)	Hypo-γ (age in years at diagnosis)	Chronic colitis (age in years at diagnosis)	Other manifestations (age in years at diagnosis)	Outcome (age in years)
X1.1	E99KfsX129		5	+	?	?	–	–	?	Alive, well (8)
X1.2	E99KfsX129	–	5.3	+	?	+ (5)	–	–	?	Alive, well (11)
X1.3	E99KfsX129		2.5	+	?	+ (2.5)	+	–	?	Alive, well, IVIG (14)
X1.4	E99KfsX129	–	7.8	+	+	+ (6)	–	+ (4)	Cholangitis (23)	Alive, ileitis (23)
X1.5	E99KfsX129		3	+	+	+ (3)	–	–	–	Alive, well (30)
X1.6	E99KfsX129	–	0.8	– (HHV-6+/–)	+ (EBV+)	+ (1)‡	+(10)	–	–	HSCT (11), died (11)
X1.7	ND		1.5†	?	+	+ (1.5)‡	+(42)	+ (41)	Cholangitis (41)	Died (42, colitis)
X2.1	I397FfsX414	–	1.2	+	+	+ (1)‡	–	–	–	HSCT (1.6), died (d+13, HLH)
X3.1	E118X	–	23	+	+	+ (22)	+(22)	–	–	Alive, well, IVIG (39)
X3.2	ND		0.5	?	–	?	?		–	Died (0.5, HLH)
X3.3	ND		20	+	–	?	?		–	Died (20, HLH)
X3.4	E118X	–	–	NA	–	+ (7)	–	–	–	Alive, well, SM (10)
X4.1	del. of exon 2	–	20	+	+ (21,EBV+)	+ (1)‡	–	–	–	Alive, well (28)
X4.2	del. of exon 2	–	10	?	+ (11, EBV+)	+ (6)‡	–	–	–	Alive, well (15)
X5.1	D130GfsX140	–	2.5	+	+ (3.4-3.6)	+ (1)	–	–	–	HSCT (3.6), died (4)
X5.2	ND		0.1	?	–	?	?	–	–	Died (0.1, HLH)
X5.3	ND		3.5	+	–	?	?	–	–	Died (3.5, HLH)
X6.1	R238X	–	1.7	+	+	+‡	–	–	–	Alive, recurrent HLH (3)
X7.1	I397NfsX405	–	2.7	+	+ (3.2-3.5, EBV+)	+ (2.7)	–	–	–	Alive, recurrent HLH (3.5)
X8.1	E434AfsX457	+/–	15.5	+	–	–	–	–	–	Alive, well (16)
X9.1	G466X	+/–	8†	+	–	+ (8)‡	+ (8)§	–	–	Alive, well, SM (27)
X9.2	G466X	+/–	–	NA	–	+ (21)	+ (21)§	–	–	Alive, well, SM (30)
X9.3	G466X	+/–	–	NA	–	+ (4)‡	–	+ (12)	Recurrent infections	Alive, colitis (14)
X9.4	G466X	+/–	–	NA	–	+ (22)‡	+ (10)§	–	Chronic liver failure (22)	Died (29, liver failure), IVIG,
X9.5	G466X	+/–	–	NA	–	–	–	–	–	Alive, well (39)
X9.6	ND		–	NA	–	?	?	+	?	Died (27, colitis)
X9.7	ND		–	NA	–	+‡	?	–	Recurrent infections	Died (52, pneumonia)
X10.1	T470S	+	8†	– (HSV-1+)	–	–	+ (4)§	–	Cryptococcosis (4)	Alive, well, IVIG (8)
X11.1	R381X	–	0.9†	–	NA	+ (0.6)‡	–	–	–	HSCT (1.2), died (1.4)
X11.2	ND		?	?	?	?	?	+(4)	?	Died (4, colitis)

SM indicates recurrent splenomegaly or hepatosplenomegaly; Hypo-γ, hypogammaglobulinemia; ?, unknown; HSCT, hematopoietic stem cell transplantation; ND, not done; NA, not applicable; and del., deletion.

*Patient identification: X indicates XIAP deficiency, the first number corresponds to the family and the second to the individual patient; + indicates yes or positive; –, no or negative; and +/–, weakly positive.

†Diagnosed as incomplete HLH.

‡Recurrent splenomegaly or hepatosplenomegaly associated with intermittent fever, anemia, and cytopenia.

§With recurrent respiratory infections.

relapsed in 2 of 7 SAP-deficient HLH-survivors (29%), whereas 11 of 14 XIAP-deficient HLH-survivors (79%, 3 unknown) had ≥ 1 relapse of HLH ($P = .055$).

Six of the 18 SAP-deficient patients with HLH (33%) had proven neurologic involvement with mostly (5 of 6, 83%) lethal outcome, whereas 2 of 22 of XIAP-deficient patients with HLH (9%) had neurologic involvement with less mortality (1 of 2, 50%).

EBV infection was the most-frequent identified trigger of the first HLH episode in the SAP-deficient (11 of 12, 92%, 6 unknown) and XIAP-deficient (15 of 18, 83%, 4 unknown) patients ($P = .63$) (Table 3). Only PS13.1, PX1.6, PX10.1, and PX11.1 had a first HLH episode in the absence of a proven EBV-infection, whereas the EBV status of 6 SAP-deficient patients and 4 XIAP-deficient patients is not known. PX1.6 and PX4.2 subsequently experienced an HLH-relapse with positive EBV polymerase chain reaction. In 2 patients, herpes simplex virus type 1 (HSV-1) and human herpesvirus type 6 (HHV-6) were detected in the blood by polymerase chain reaction in the course of their first HLH episode. Of note, in several XIAP-deficient patients, other viruses than EBV were tested, including cytomegalovirus, parvovirus B19, HSV, HHV-6, HHV-8, HIV, human T-cell leukemia virus, adenovirus, and varicella-zoster virus. All were negative.

Splenomegaly and incomplete forms of HLH

Recurrent splenomegaly occurring in the absence of systemic HLH and often associated with fever and cytopenia (consisting of pancytopenia, bicytopenia, thrombocytopenia, and anemia) was frequently observed in XIAP-deficient patients (20 of 23, 87%, 7 unknown), whereas it was only found in 2 of 29 SAP-deficient patients (7%, 4 unknown; $***P < .0001$; Table 3). In 8 XIAP-deficient patients, episodes of splenomegaly occurred before they developed HLH and were the first clinical sign of the disease. Overall, although 3 patients with splenomegaly up to now did not