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Metabolic Syndrome and Cardiovascular Risk Factors after Hematopoietic Cell Transplantation in Severe Mucopolysaccharidosis Type I (Hurler Syndrome)

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A B S T R A C T

Hematopoietic cell transplantation is a life-saving procedure, but one associated with increasing long-term cardiovascular risk requiring frequent long-term follow-up. This therapy has significantly lengthened survival in mucopolysaccharidosis type IH (Hurler syndrome), a disease with known coronary artery involvement. Metabolic syndrome—a constellation of central obesity, high blood pressure, low high-density lipoprotein cholesterol, elevated triglycerides, and fasting blood glucose—is associated with increased cardiovascular risk, and occurs when any 3 or more of these 5 components is present within a single individual. The incidence of metabolic syndrome and its components is poorly defined after transplantation for Hurler syndrome. Chart review of all long-term survivors of hematopoietic cell transplantation for Hurler syndrome ≥9 years of age for factors comprising the metabolic syndrome: obesity, high blood pressure, low high-density lipoprotein cholesterol, elevated triglycerides, and fasting blood glucose. Sixty-three patients were evaluated, 20 of whom had components of the metabolic syndrome available for review. There was no significant difference in age at transplantation, sex, number of transplants, pretransplant radiation, or percent engraftment between those with and without these data. Median follow-up after transplantation for the 20 patients with data was 14.3 years. Only 1 (5%) patient of this group fulfilled the criteria for metabolic syndrome. Fifty-three percent of the patients had 1 or more components of metabolic syndrome: the most common was high blood pressure occurring in 40%. Metabolic syndrome is uncommon in this cohort of long-term survivors of hematopoietic cell transplantation for Hurler syndrome but almost half of the patients had 1 or more components of the syndrome, with high blood pressure being the most common. Further studies are needed to develop guidelines in this diagnosis as well as other nonmalignant diseases of children.

INTRODUCTION

Annually, more than 20,000 hematopoietic cell transplantation (HCTs) are performed in the United States for malignant as well as nonmalignant (often rare) diseases of childhood [1]. Long-term survivors of HCT are at an increased risk of death from long-term sequelae as well as increased risk of cardiovascular disease [2]. Current international guidelines recommend frequent monitoring of long-term survivors for the development of metabolic syndrome (MetS) [3,4]—a constellation of central obesity, high blood pressure, low high-density lipoprotein (HDL) cholesterol, elevated fasting blood glucose, and triglycerides—that is associated with increased cardiovascular risk [5-9]. When any 3 or more of these metabolic factors are present, the diagnosis of MetS is made. The existing international guidelines have been developed for long-term survivors of HCT performed predominantly for malignancies. Recognition that late effects may be different after HCT for nonmalignant diseases, and developing guidelines for these diseases, is a work in progress [10-12].

Severe mucopolysaccharidosis (MPS) type IH (Hurler syndrome) is a genetically inherited, multisystem disorder that is well recognized as being lethal within the first decade of life if untreated [13]. Extensive cardiac involvement, including the presence of early, diffuse coronary artery narrowing from myointimal proliferation, is a common feature of untreated severe MPS IH [14] and is thought to be responsible for as many as 50% of the deaths in untreated children [15]. HCT has been a reported therapy for MPS IH since 1980 [16] and has favorably affected the natural history of the disease, with individuals who now survive well into adulthood [17].

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Given the underlying coronary artery pathology, an increased incidence of cardiovascular risk may be expected after HCT, but sudden and unexpected death actually occurs infrequently in long-term survivors of HCT with Hurler syndrome [17]. However, the incidence of MetS is unknown in this population.

We report herein the detailed findings in 20 patients with severe MPS IH more than a decade after HCT to provide guidance for the need for follow-up after HCT.

STUDY DESIGN AND PATIENT POPULATION

This study was approved by the Human Research Protection Program of the University of Minnesota (1608M92702). Individuals with MPS IH who had undergone previous HCT were identified through the existing University of Minnesota Bone Marrow Transplant Registry. Based on national pediatric guidelines recommending universal lipid screening of all children between 9 and 11 years of age [18], patients who had survived to 9 years of age after HCT had the following data collected: sex, age at transplantation, number of transplants, presence of pre-HCT radiation, most recent percentage engraftment, survival, height, weight, blood pressure and laboratory values for fasting lipid profile (total, HDL, non-HDL, and/or low-density lipoprotein cholesterol; triglycerides; and fasting blood glucose). Laboratory values were obtained at annual follow-up visits, most commonly from 2014 onward. Many patients were unable to either obtain insurance approval and/or have the means to travel to our center for follow-up after HCT. This resulted in a group of patients, known to be alive through registry contact, who did not undergo these evaluations. The demographics of these patients were compared with those whom we had studied.

DETERMINATION OF METS

For all individuals ≥18 years of age with data, body mass index (BMI) was calculated from measured height and weight using the BMI calculator app constructed by the National Institutes of Health [19]. Because of the retrospective nature of the study, waist circumference was not available and BMI was used as to classify obesity status, as recommended by earlier studies involving adolescents [20]. For adolescents under age 18 years, BMI was calculated from measured height and weight using the BMI percentile calculator app for children and teens constructed by the Centers for Disease Control and Prevention [21]. BMI values ≥30 kg/m^2 in adults or ≥95th percentile for age/sex in adolescents were considered obese [22]. Blood pressures >130/85 in adults or >90th percentile for height in those <18 years of age by the National Health and Nutrition Examination Survey were deemed hypertensive [23]. Abnormal HDL cholesterol, fasting triglycerides, and blood glucose values were noted in accordance with Adult Treatment Panel III guidelines [24] as modified by 2009 harmonizing guidelines [25]. Diagnosis of MetS was fulfilled for any individual by the presence of at least 3 of 5 published criteria (Table 1).

STATISTICAL ANALYSIS

Comparison of sex, age at transplant, radiation status, survival, and percentage engraftment was made between those who had data related to the MetS available and those who did not. Categorical factors were compared by the chi-square test and age by the unpaired *t* test. Survival was calculated by Kaplan-Meier estimates. Comparison of curves was completed by the log-rank test. For those in whom data related to the MetS was available, the previous comparisons were repeated between patients who received radiation and those who had not. All reported *P* values were 2 sided. All analyses were performed using SAS 9.4 (SAS Institute, Inc., Cary, NC) and QuickCalcs, GraphPad Prism (version 7; GraphPad Software, La Jolla, CA).

RESULTS

One hundred fifty individuals with severe MPS IH have undergone HCT since the inception of our program until January 31, 2017, with 91 current survivors. Of these survivors, 63 were ≥9 years of age. Data related to the MetS were available in 20 (32%) of these 63 age-censored survivors (Table 2).

There were no statistically significant differences with respect to gender, age at transplant, number of transplants, administration of pre-HCT radiation, or percentage engraftment between the study cohort (n = 20, with lipid profile data) and those in whom testing had not been performed. Those without data had better survival at 20 years post-HCT than did those with metabolic data (100% versus 82%; $P = .03$).

For the 20 individuals in whom data related to the MetS were available there were no statistically significant differences in sex, average age at lipid testing, or overall survival between those who had received pre-HCT radiation or those who had not (data not shown). As pre-HCT radiation was utilized primarily for those requiring second HCTs, there were significant differences in the following variables: number of patients requiring 2 transplants (0 of 11 patients without radiation versus 4 of 9 patients with radiation; $P = .03$), the age at last transplant (12.8 ± 4.5 months without radiation versus 25.9 ± 14.7 months with radiation; $P = .01$) and percentage engraftment ≥90% (5 of 11 of those without radiation versus 8

Table 1
MetS Definitions Used in This Publication

Risk factor component	Adult cutoff points (reference)*	Adolescent cutoff points (reference)
Abdominal obesity†	Waist circumference [24]	Waist circumference [23]
Male, cm	>102	≥90th percentile
Female, cm	>88	≥90th percentile
Low HDL cholesterol		
Male, mg/dL	<40 [24]	≤40 [23]
Female, mg/dL	<50 [25]	≤40 [23]
Elevated fasting blood glucose, mg/dL	≥100 [25]	≥110 [23]
Elevated triglycerides, mg/dL	≥150 [24]	≥110 [23]
High blood pressure, mm Hg	≥130/85 [24]	≥90th percentile [23]

* Adult values for low HDL cholesterol and fasting blood glucose are taken from a task force that harmonized Adult Treatment Panel III cutoff points with values that had previously been utilized by several national organizations [25].

† BMI was used as a surrogate marker of obesity, as waist circumference was not available in this retrospective study [20] with obesity defined as BMI ≥95th percentile [22].

Table 2
Comparison of HCT Information in Patients with Severe MPS (≥9 Years of Age) Who Did and Did Not Have Lipid Laboratory Data

Factor	With metabolic data	Without metabolic data	*P* value
Sex			.26
Male	15 (75)	26 (60)	
Female	5 (25)	17 (40)	
Average age at HCT, mo	18.7	21.3	.42
HCT number			.38
1	16 (80)	38 (88)	
2	4 (20)	5 (12)	
TBI/TLI			.81
No	11 (55)	25 (58)	
Yes	9 (45)	18 (42)	
Survival from HCT (Kaplan-Meier)			.03
5 yr, %	100	100	
10 yr, %	100	100	
15 yr, %	100	100	
20 yr (95% CI), %	82 (45-95)	100	
Engraftment			.21
<10%	0	2 (5)	
10–89%	7 (35)	6 (14)	
≥90%	13 (65)	35 (81)	

Data are presented as n (%), unless otherwise indicated.
CI indicates confidence interval; TBI, total body irradiation; TLI, total lymphoid irradiation.

of 9 with radiation; $P = .05$). The amount of radiation received varied from 200 to 1400 cGy, with 6 of the 9 patients receiving 750 to 1400 cGy.

The overall median age at the time when clinical and laboratory data was obtained was 18.4 (range, 9.9 to 30.2) years of age. Laboratory data were obtained at a median value of 15.5 (range, 4.9 to 28.4) years after HCT in 19 of 20 patients. One patient who underwent a second HCT for an unrelated reason was studied at 1.9 years after the second HCT.

Preconditioning regimens and donor sources were similar in those with and without pre-HCT radiation (Table 3). Most often pre-HCT conditioning consisted of administration of either busulfan and Cytoxan or busulfan and Cytoxan with antithymocyte globulin or prednisone (15 of 20 patients [75%]). Donor source was related marrow (10 of 24 HCTs [42%]), unrelated marrow (8 of 24 HCTs [33%]), or cord blood (6 of 24 HCTs [25%]). Post-HCT regimens at the time of study included enzyme replacement therapy (1 of 11 [9%] patients without pre-HCT radiation and 2 of 9 [22%] patients with pre-HCT radiation) and cyclosporine in 1 patient).

Overall, only 1 of the 20 individuals, an adolescent who had received pre-HCT total body irradiation and was partially engrafted, fulfilled the criteria for MetS consisting of hypertension, obesity, decreased HDL cholesterol, and elevated triglycerides (Table 4). One other patient, who did not fulfill the criteria for MetS, but had a strong family history of cardiovascular disease, had elevated total and low-density lipoprotein cholesterol and was treated with a statin.

Despite the low incidence of MetS, 10 of 19 (53%) of the remaining individuals had 1 or more MetS components associated with MetS. These isolated MetS components occurred both in patients with (4 of 9 [44%]) and without (6 of 11 [55%]) pre-HCT radiation. The most common MetS component for all individuals in this study was high blood pressure, occurring in at least 8 of 19 patients (43%, 1 patient missing measurement). Recorded blood pressure values were just >90th percentile in 5 of 9 patients <18 years of age; >130 mm Hg but <140 mm Hg systolic in 2 of the 10 adult patients, and markedly elevated at 146/100 mm Hg in 1 of the remaining adult patients. Angiotensin-receptor blockade was being administered to 6 of 11 (54%) of those patients without radiation and 1 of 9 (11%) of those patients with pre-HCT radiation ($P = .07$) at the time of study. Renal function was normal in all 20 patients at the time of study with maximum values for blood urea nitrogen and creatinine of 24 and 1.0 mg/dL, respectively (data not shown).

Table 3
Conditioning Regimens and Donor Sources in Patients with Metabolic Data after HCT for Severe MPS IH

Peri-HCT factors	No radiation (n = 11)	Radiation (n = 9)
Conditioning regimen	Bu/Cy/ ± ATG (4) Bu/Cy/ATG/prednisone (6) Bu/Cy/Campath (1)	Bu/Cy/ ± ATG (3) Bu/fludarabine (1) Patients with 2 HCTs: • Bu/Cy/ ± ATG (1) • Cy/ATG; Bu/Cy/ATG (2) • Bu/Cy/prednisone/ATG; Cy/fludarabine/ATG (1) • Bu/Cy; melphalan/Campath/clofadarabine (1)
Donor source	Related marrow (5) Unrelated marrow (2) Unrelated cord (4)	Related marrow (2) Unrelated marrow (1) Patients with 2 HCTs: • Related marrow, related marrow (1) • Unrelated marrow; unrelated marrow (2) • Unrelated cord; unrelated marrow (1) • Related marrow; unrelated cord (1)

ATG indicates antithymocyte globulin; Bu, busulfan; Cy, Cytoxan.

Table 4
Summary of MetS Factors in Patients after HCT for Severe MPS I

Factor	Without radiation	With radiation	*P* value
Age at lab visit (months)	212	223	.75
Obesity by BMI	1/11	1/9	1.000
Abnormal HDL cholesterol	1/11	3/9	.29
Elevated triglycerides	1/11	1/9	1.000
Elevated fasting blood glucose	1/11	0/8	1.000
High blood pressure	4/11	4/8	.66
MetS Factors			
0	5/11	4/9	
1	4/11	3/9	
2	2/11	1/9	
3 +	0/11	1/9	.45

Other MetS components in order of decreasing occurrence included low HDL cholesterol in 4 of 20 (20%) patients, elevated triglycerides levels in 2 of 20 (10%) patients, obesity in 2 of 20 (10%) patients, and elevated fasting blood glucose in 1 of 20 (5%) of patients. Notable also was short stature: the height of each individual was well below the fifth percentile for age (data not shown).

DISCUSSION

Despite widespread evidence implicating HCT as a driver for increased incidence of MetS, in this study of adults and adolescents with severe MPS IH who have undergone HCT as infants and young children, we have found only 1 individual (5%) fulfilling the criteria for MetS after a median of 14.3 years of follow-up. This is an unexpected finding when placed within the context of a disease (severe MPS I) with known coronary artery pathology [14,26], a procedure (HCT) with reported 32% to 49% long-term risk for MetS in children/adolescents and adults [8,9,27], and the high background prevalence of MetS for adults (34.2%) and adolescents (10.1%) within the general U.S. population [28,29].

Almost half (9 of 19 [47%]) of the remaining cohort had no MetS components identified at screening. Although 10 of the remaining 19 patients (53%) did have 1 or more MetS components present, this was still not as high as the >70% incidence of 1 factor being present within the general adolescent population of naturally occurring MetS [28] or the 68% occurrence of 1 or more MetS components reported in previous studies of HCT for (mostly) malignant diseases in childhood [9,27].

The pattern of MetS components in our patients differed from naturally occurring MetS in adults where elevated blood pressure and obesity are the most common components [29] or in adolescents in which obesity alone predominates [28] (Table 5) The pattern of MetS components in our patients mirrored that found in post-HCT patients with long-term (median 14.5 years) follow-up [27] where the most common components were high triglycerides, low HDL, and high blood pressure and the second most common were obesity, low HDL, and high blood pressure [27]. Our single patient with MetS had all 4 factors present. The most common factors in the remainder of our patients were high blood pressure (43%) and low HDL cholesterol (20%); obesity (10%), elevated triglycerides (10%), and fasting blood glucose (5%) were uncommon.

High blood pressure, while common in our patients, was either mild (just greater than the 90th percentile) in the adolescents or just beyond the cutoff (>130 but <140 mm Hg systolic) in all but 1 adult patient. Full evaluation for hypertension was not undertaken in any patient, the possibility of "white coat" hypertension could not be excluded and the administration of angiotensin-converting enzyme inhibition to decrease afterload in the presence of left-sided cardiac valve regurgitation further confounded the issue.

The low incidence of MetS found in this study appears to contradict findings from other methods of studying cardiovascular risk in MPS such as measurement of carotid intima-media thickness by noninvasive imaging [30-32] and endothelial function [33]. In post-HCT MPS IH patients, carotid-intima-media thickness is increased and endothelial function decreased when compared with normal individuals [34,35], findings that suggest increased cardiovascular risk.

The strengths of the study include the single site evaluation of a unique group of patients with a rare disease who have undergone HCT and been followed for up to 28 years after HCT. Weaknesses include the potential for selection bias considering the relatively high number of patients for whom no MetS data were available. Also, we used BMI instead of waist circumference because the latter was not available in the medical chart. Finally, although the number of patients included in this study is relatively high considering the rarity of Hurler syndrome, it should be acknowledged that in absolute terms, the sample size was rather small. The equivalent survival of the larger group of HCT survivors in whom no metabolic data was available should not be construed to imply that this group also had an equally low incidence of MetS.

In summary, a small group of adolescents and adults with MPS IH, followed for a median of 14.3 years after HCT, displayed only a 5% occurrence of MetS in contrast to both naturally occurring MetS and Mets after HCT for (predominantly) cancer. Although half of the patients had at least 1 MetS component, this too was less than what has been reported in either naturally occurring or post-HCT MetS. The most common single MetS component was high blood pressure. Funding for further research on the long-term effects

Table 5
Most Common Patterns of Risk Factor Clustering in Various Types of MetS

Age group (reference)	Obesity	Low HDL	Elevated triglycerides	Elevated fasting blood glucose	High blood pressure
Naturally occurring					
Adult [29]	X	X			
Adolescent [28]	X		X		
Post-HCT (early)					
Adult [8]			X		X
Adolescent [9]		X	X		
Post-HCT (late)					
Young adult [27]		X	X		X
This study					
Adolescent/young adult		X			X

of expensive and complex therapy for children with rare diseases such as these is warranted.

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