Prevalence and risk factors of the metabolic syndrome in adult survivors of childhood leukemia

Claire Oudin,[1] Marie-Claude Simeoni,[2] Nicolas Sirvent,[3] Audrey Contet,[4] Audrey Begu-Le Coroller,[5] Pierre Bordigoni,[4] Catherine Curtillet,[1] Maryline Poirée,[3] Isabelle Thuret,[1] Barbara Play,[1] Mara Carazza Massot,[2] Pascal Chastagner,[4] Hervé Chambost,[1] Pascal Auquier,[2] and Gérard Michel[1]

[1]Department of Pediatric Hematology, Hôpital de la Timone Enfants, Marseille, France; [2]Research Unit EA 3279 and Department of Public Health, Hôpital de la Timone, Marseille, France; [3]Department of Pediatric Onco-Hematology, CHU l'Archet, Nice, France; [4]Department of Pediatric Onco-Hematology, Hôpital d'Enfants de Brabois, Vandoeuvre Les Nancy, France; and [5]Department of Endocrinology, Hôpital de la Timone, Marseille, France

We evaluate the prevalence and risk factors of the metabolic syndrome (MS) in young adults surviving childhood leukemia. During the years 2007 to 2008, assessment of MS was proposed to all adults included in the Leucémie de l'Enfant et de l'Adolescent program, a French prospective multicentric cohort of leukemia survivors. Among 220 eligible patients, 184 (83.6%) had complete evaluation. Median age at evaluation and follow-up duration were 21.2 and 15.4 years. Overall prevalence of MS was 9.2% (95% confidence interval, 5.5-14.4). There was no association of MS with sex, age at diagnosis, leukemia subtype, steroid therapy, and central nervous system irradiation. Patients were stratified according to 4 therapeutic modalities: chemotherapy alone (n = 97), chemotherapy and central nervous system irradiation (n = 27), hematopoietic stem cell transplantation (HSCT) without (n = 17) or with (n = 43) total body irradiation (TBI). MS occurred in 5.2%, 11.1%, 5.9%, and 18.6% of them, respectively. The higher risk observed in the HSCT-TBI group was significant in univariate and in multivariate analysis (odds ratio [OR] = 3.9, *P* = .03). HSCT with TBI was associated with a higher rate of hypertriglyceridemia (OR = 4.5, *P* = .004), low level of high-density lipoprotein cholesterol (OR = 2.5, *P* = .02), and elevated fasting glucose (OR = 6.1, *P* = .04) So, TBI is a major risk factor for MS. Further studies are warranted to explain this feature. (*Blood*. 2011;117(17): 4442-4448)

Introduction

Along with the improving childhood leukemia survival rate, long-term life-threatening complications are increasingly reported.[1-5] Cardiovascular morbidity and mortality have particularly been highlighted for cancer survivors.[2,6] The Childhood Cancer Survivor Study assessed that cancer long-term survivors were 8.2 times more likely to die of cardiac-related events than the standard population[2] and were more likely to develop coronary artery disease and cerebrovascular events than healthy siblings (relative risk = 10.4 and 9.3, respectively).[3]

Cardiovascular conditions are major causes of morbidity and mortality in our countries. The metabolic syndrome (MS), defined as a constellation of cardiovascular risk factors, is highly associated with cardiovascular events and death.[7,8] An increased risk of MS or its components has already been shown among cancer survivors,[6,9-13] but few studies use international validated MS definitions in homogeneous cohorts.[14,15] Although several authors have pointed out cranial irradiation as a major risk factor for development of MS,[6,10,11,16] little is known about other risk factors.[17]

Here we attempt to determine the frequency of the MS as defined by the National Cholesterol Evaluation Program (NCEP) Adult Treatment Panel III (ATP III)[14] and its components in a multicentric prospective cohort of acute leukemia adult survivors treated during childhood. We also aim to describe risk factors associated with an increased rate of MS in this population.

Methods

Patients

This prospective study was designed to evaluate prevalence and risk factors for the MS in young adult leukemia survivors included in the Leucémie de l'Enfant et de l'Adolescent program (LEA). This French multicentric program was created in 2003 to evaluate prospectively the long-term health status, quality of life, and socioeconomic status of childhood leukemia survivors who were enrolled in treatment from 1980 to present in 2 geographic areas (PACA-Corse and Lorraine). Details of the whole program have been previously described.[18] During the years 2007 and 2008, assessment of MS was systematically proposed to all adults with a new LEA health status evaluation. Among 220 eligible patients, 184 (83.6%) had a complete evaluation for the MS and are the subjects of this report (Figure 1). All have signed informed consent in accordance with the Declaration of Helsinki. The study was approved by the French National Program for Clinical Research and the Institut National du Cancer.

Study evaluation

The MS was defined according to the NCEP-ATPIII revised in 2005.[14] Among the different definitions of MS, this one was chosen because of its clinical applicability and reliability.[19] Patients were defined as having the MS when they met at least 3 of 5 criteria: (1) elevated waist circumference (≥ 102 cm in men, ≥ 88 cm in women); (2) elevated blood pressure

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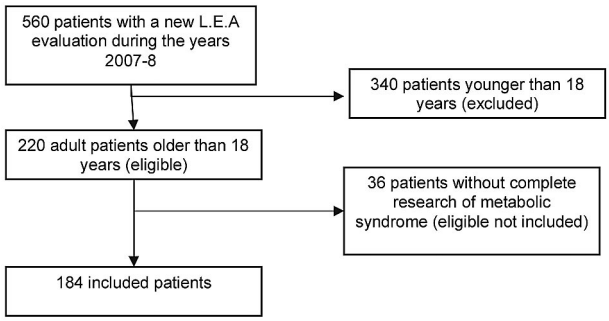

Figure 1. The LEA cohort. Thirty-six patients did not benefit from a complete research for the metabolic syndrome.

(systolic blood pressure ≥ 130 mmHg and/or diastolic blood pressure ≥ 85 mmHg and/or treatment); (3) reduced high-density lipoprotein (HDL) cholesterol (< 40 mg/dL [1.03mM] in men, < 50 mg/dL [1.3mM] in women); (4) elevated fasting glucose (≥ 1 g/L [5.5mM] or drug treatment for elevated glucose); and (5) elevated triglycerides (≥ 150 mg/dL [1.7mM] or drug treatment for elevated triglycerides).

Blood pressure was measured using a sphygmomanometer. Abdominal circumference was evaluated at midway between the iliac crest and the last rib. Blood samples for fasting glucose, triglycerides, and HDL cholesterol were obtained after fasting overnight.

Growth hormone (GH) deficiency (GHD) was detected by measuring insulin-like growth factor I plasma levels and GH peak response to at least 2 stimulation tests per patient. These tests were insulin tolerance tests (0.05 IU/kg intravenously), GH-releasing hormone infusion tests (80 mg, Somatoline intravenously, Choay/Sanofi) or propanol-glucagon tests (0.25 mg/kg oral propanolol and 1 mg glucagon intramuscularly). GHD was diagnosed when peak GH levels after stimulation were less than 20 mIU/L (or 10 ng/mL). The tests were performed at least 6 months away from any antileukemic treatment. We did not use priming with sex hormones before these tests. Evaluation was done only for patients with decreased height growth velocity.

Hypogonadism was defined by low testosterone (males) or estradiol (females) serum level and classified as hypergonadotrophic or hypogonadotrophic according to luteinizing hormone and follicle-stimulating hormone values. Normal hormonal levels were defined according to the age at evaluation and the norms of each hospital laboratory. Evaluation was done for patients who underwent stem cell transplantation and/or who had pubertal delay.

Thyroid function analysis was performed only for patients who underwent stem cell transplantation or central nervous system (CNS), mediastinal, or cervical irradiation. A diagnosis of subclinical hypothyroidism was made if thyroid-stimulating hormone level was high and thyroxine level normal, whereas overt hypothyroidism was diagnosed in patients with low thyroxine and high thyroid-stimulating hormone level.

Statistical analysis

Statistical analysis was performed using SPSS, Version 15.0 (SPSS) and SAS, Version 9.1. Qualitative data were expressed as x/y (percentages), y being the denominator. The denominator was not mentioned when it referred to the global population (n = 184). Quantitative data were shown as median (range). χ^2 and Fisher exact test were used to compare qualitative variables. Quantitative variables were compared using the Student *t* test or the Mann-Whitney test. Prevalence rates of MS and its components are reported with 95% confidence interval (CI). Multivariate logistic regression analyses were used to construct models of association between the occurrence of the MS and its components (as the dependent variables) and potential risk factors (as the explanatory variables). Odds ratios (ORs) were estimated with their 95% CI, and the significance threshold was set as $P < .05$.

Results

Eligible patients, comparison between participants and nonparticipants

During the study period, 220 patients more than 18 years of age fulfilled all the selection criteria and were included in the LEA cohort. Of the 220, research of MS was completed in 184 patients (83.6%) who finally participated in the present study. There was no significant difference between those 184 included patients and the 36 remaining with regard to sex, age and weight at diagnosis of acute leukemia, type of leukemia, age and weight at evaluation of the MS, and type of treatment (transplantation, irradiation, and type of chemotherapy) as well as treatment-related complications (graft-versus-host disease, late endocrine complications).

Characteristics of studied cohort

Median age at evaluation of MS was 21.2 years (range, 18-41 years); median follow-up was 15.4 years (range, 3.4-30.2 years) (Table 1). As expected, the majority (81.5%) of the patients had been diagnosed for acute lymphoblastic leukemia (ALL).

Patients had been treated according to various French multicentric protocols (ie, FRALLE [French Acute Lymphoblastic Leukemia], EORTC [European Organization for Research and Treatment of Cancer] and LAME [Leucemie Aigue Myeloblastique Enfant]) depending on the period of their treatment and type of leukemia.[20-24]

Ninety-seven patients (52.7%) had received chemotherapy only, 27 (14.7%) chemotherapy and CNS irradiation, and 60 (32.6%) hematopoietic stem cell transplantation (HSCT). The use of CNS irradiation had been based on the underlying disease status and the protocol in use at the time of leukemia treatment. Irradiation dose was 18 or 24 Gy in 74.1% and 18.5% of the cases, respectively (unknown, 7.4%).

Total body irradiation (TBI) had been used in 43 (71.7%) of allografted or autografted patients. None of the transplanted subjects who underwent TBI as HSCT conditioning regimen had been previously treated with CNS irradiation. TBI had been administered fractionated, usually as 2 Gy twice daily for 3 days for a total dose of 12 Gy with lung shielding at 8 Gy.

Allogeneic transplantation accounted for 65% of the transplantations. Donor type included 27 matched related donors (69.2% of the allogeneic transplantations), 4 matched unrelated donors (10.3%), 2 mismatched related donors (5.1%), and 6 cord bloods (15.4%). Finally, steroids and asparaginase have been used in all 150 children with ALL.

Frequency and risk factors for the MS in the LEA cohort

Of the 184 patients enrolled, 17 patients met the criteria for the MS (9.2%, 95% CI, 5.5-14.4). The frequency of each component of the MS is described in Table 2.

In the univariate analysis, variables significantly associated with a higher risk of metabolic syndrome were a history of TBI (18.6% vs 6.4%, $P = .015$) and an older age at time of evaluation (median age, 22.2 years in patients with the MS vs 21.1 years among unaffected subjects, $P = .05$). There was a trend toward a higher risk of MS among patients who had received HSCT (15.0% of transplanted patients vs 4.4% of nontransplanted patients), but this difference did not reach the threshold of statistical significance ($P = .06$). We did not detect any significant influence of sex, age at diagnosis, leukemia subtype (acute myeloid leukemia vs ALL),

Table 1. Patient characteristic (n = 184)

Characteristics	Value, no. (%) or mean ± SD
Sex ratio, males/females	95 (51.6)/89 (48.4)
Age at diagnosis of acute leukemia, y	7.9 (0.5-18)
BMI at diagnosis of acute leukemia, kg/m^2	16.0 (12.4-24.9)
Age at evaluation of MS, y	21.2 (18-41)
BMI at evaluation of MS, kg/m^2	22.1 (15.9-39.1)
Type of leukemia, no. (%)	
ALL	150 (81.5)
AML	34 (18.5)
Therapy for leukemia, no. (%)	
Chemotherapy without irradiation	97 (52.7)
Chemotherapy with CNS irradiation	27 (14.7)
Involved fields	
Cranial irradiation, no. (%) of CNS irradiation	22/27 (81.5)
Craniospinal irradiation, no. (%) of CNS irradiation	5/27 (12.5)
Irradiation dose	
18 Gy, no. (%) of CNS irradiation	20/27 (74.1)
24 Gy, no. (%) of CNS irradiation	5/27 (18.5)
Unknown, no. (%) of CNS irradiation	2/27 (7.4)
Stem cell transplantation	60 (32.6)
Allogeneic stem cell transplantation, no. (%) of transplanted patients	39/60 (65.0)
Autologous stem cell transplantation, no. (%) of transplanted patients	21/60 (35.0)
Total body irradiation, no. (%) of transplantation recipients	43/60 (71.7)
Steroid therapy (any time)	162 (88.0)
Transplantation-related complications, no. (%) of allogeneic recipients	
Acute GVHD grade ≥ 2 or chronic extensive GVHD	18/39 (46.2)
Post-transplantation steroid	32/39 (82.1)
Endocrine late side effects	
Hypogonadism	36 (19.6)
Hormonal substitutive therapy, no. (%) of patients with hypogonadism	28/36 (77.8)
Growth delay	11 (6.0)
GH therapy, no. (%) of patients with growth delay	5/11 (45.5)
Hypothyroidism, no. (%) of transplantation or irradiated patients	15 (19.1)
Substitutive therapy, no. (%) of patients with hypothyroidism	15/15 (100)
Obesity (BMI ≥ 30 kg/m^2)	10 (5.7)
Overweight (BMI, 25-29.9 kg/m^2)	38 (20.6)
Medication at evaluation	
Insulin/lipid-lowering agent/antihypertensive, no. (%) of MS patients	1/17 (5.9)

BMI indicates body mass index; AML, acute myeloid leukemia; and GVHD, graft-versus-host disease.

steroid therapy (yes vs no), and CNS irradiation. In addition, in the transplantation group, the prevalence of MS did not significantly differ according to the kind of transplant (autotransplant vs allotransplant) and to whether or not the patient experienced graft-versus-host disease.

Patients were then stratified into 4 groups according to the therapeutic modalities they had received: chemotherapy only, chemotherapy and CNS irradiation, HSCT without TBI, and HSCT with TBI. The frequency of MS among each of these groups was 5.2%, 11.1%, 5.9%, and 18.6%, respectively. Using a logistic regression model with the chemotherapy group as the reference, we found that ORs for occurrence of the MS were 2.3 for the group with chemotherapy and CNS radiation (not significant), 1.2 for HSCT without TBI (not significant), and 4.2 for patients who received HSCT with TBI as conditioning regimen (95% CI, 1.3-13.7, $P = .01$).

For the multivariate analysis, leukemia subtype, sex, age at evaluation, and the treatment modality as a 4 class covariate were included in the model. Age at leukemia diagnosis was strongly correlated to age at evaluation, explaining that these 2 variables could not be included together in the model. As shown in Table 3, HSCT with TBI was the only covariate significantly associated with a higher risk of MS (OR = 3.9; $P = .03$).

Table 2. Prevalence rate of the MS and its components (n = 184)

	No. (%) of subjects (n = 184)	95% CI of the population
MS NCEP-ATPIII	17 (9.2)	5.5-14.4
Reduced HDL cholesterol	55 (31.8)	24.9-39.3
Elevated triglycerides	24 (13.0)	8.5-18.8
Elevated fasting glucose	10 (5.7)	2.8-10.3
Elevated blood pressure	41 (25.3)	18.8-32.7
Elevated waist circumference	22 (14.5)	9.2-21.0

Frequency and risk factors for the components of the MS

The frequency of each component was: elevated waist circumference, 14.5%; elevated blood pressure, 25.3%; low HDL cholesterol, 31.8%; elevated triglyceride level, 13.0%; and elevated fasting glucose, 5.7% (Table 2). Ninety-seven (25.7%) had at least one component of the MS; 36 (19.6%) had 2 or more.

Table 4 shows the impact of HSCT with TBI in a multivariate analysis, which takes into account the same factors as described before (ie, leukemia subtype, gender, age at evaluation and treatment modality). Patients who underwent HSCT after a conditioning regimen with TBI were more likely to develop abnormal lipid parameters, specifically reduced HDL cholesterol (adjusted

Table 3. Multivariate logistic regression analyses: risk factors associated with MS

	Subjects with MS, n (%) n = 184	Adjusted OR (95% CI)	*P*
Treatment modality			
No transplantation, no CNS irradiation (referent)	5 (5.2)		
No transplantation, with CNS irradiation	3 (11.1)	1.7 (0.3-9.0)	.51
Transplantation without TBI	1 (5.9)	1.1 (0.1-14.1)	.96
Transplantation with TBI	8 (18.6)	3.9 (1.1-13.3)	.03
Type of leukemia			
AML	3 (8.8)		
ALL	14 (9.3)	0.97 (0.2-4.8)	.97
Sex			
Female (referent)	9 (10.1)		
Male	8 (8.4)	0.7 (0.2-2.0)	.48
Age at evaluation (y)	NA	1.1 (1.0-1.2)	.13

NA indicates not applicable.

OR = 2.5; 95% CI, 1.1-5.7; $P = .02$), and elevated triglycerides (adjusted OR = 4.5; 95% CI, 1.6-12.5; $P = .004$). The role of TBI was also highly significant for elevated fasting glucose (adjusted OR = 6.1; 95% CI, 1.1-33.5; $P = .04$). By contrast, TBI had no impact on either abdominal circumference or elevation of blood pressure (Table 4). Of note, male subjects had a significantly higher risk of developing hypertension (OR = 3.1; 95% CI, 1.5-6.7; $P = .003$), compared with female subjects.

Association between MS and other endocrine complications

In our cohort, only 11 subjects (6.0%) were found to have GHD. GHD was not associated with a higher rate of the MS (only 2 patients among the 11 had also a MS) or with a perturbation of any component of the MS.

By contrast, the MS was more frequent among patients having hypogonadism: 8 patients of 36 (22.2%) versus 9 of the 148 remaining subjects (6.1%) ($P = .003$). Factors accounting for this difference included an increased fasting glucose and elevated triglycerides, which are significantly more frequent in patients with hypogonadism (respectively, 15.6% vs 3.5%, $P = .02$, and 27.8 vs 9.5%, $P = .003$).

Hypothyroidism tended to be associated with the MS: 4 patients of 15 (23.5%) versus 13 (7.8%) of the 169 patients without hypothyroidism ($P = .06$). Elevation of the triglycerides and low HDL cholesterol were more common among patients with hypothyroidism (41.2% vs 10.2%, $P = .0003$ and 62.5% vs 28.7%, $P = .006$, respectively).

Discussion

Overall frequency of the MS

We report a high frequency of the MS among young survivors of childhood acute leukemia: 9.2% of our cohort have a MS (8.4% males, 10.1% females). Compared with large French studies that have explored the prevalence of the MS in France, the frequency of the MS in our young patients (mean age, 22.7 years) is about twice as high as in the general population. The prevalence of the MS

Table 4. Multivariate logistic regression analyses: risk factors associated with reduced HDL cholesterol, elevated triglycerides, elevated fasting glucose, elevated waist circumference, and high blood pressure

	Reduced HDL cholesterol		Elevated triglycerides		Elevated fasting glucose		Elevated waist circumference		Elevated blood pressure	
	Adjusted OR (95% CI)	*P*	Adjusted OR (95% CI)	*P*	Adjusted OR (95% CI)	*P*	Adjusted OR (95% CI)	*P*	Adjusted OR (95% CI)	*P*
Treatment modality										
No transplantation, no CNS irradiation (referent)										
No transplantation, with CNS irradiation	1.3 (0.5-3.3)	.65	1.2 (0.3-5.9)	.63	2.4 (0.3-22.2)	.44	1.5 (0.4-6.2)	.55	0.8 (0.3-2.3)	.63
Transplantation without TBI	2.4 (0.6-9.6)	.21	0.7 (0.1-7.7)	.77	NA	.98	2.0 (0.3-13.5)	.50	0.3 (0.1-1.2)	.08
Transplantation with TBI	2.5 (1.1-5.7)	.02	4.5 (1.6-12.5)	.004	6.1 (1.1-33.5)	.04	1.0 (0.3-3.2)	.93	0.8 (0.3-2.0)	.64
Type of leukemia										
AML (referent)										
ALL	1.3 (0.5-3.7)	.57	1.0 (0.3-3.4)	.95	0.5 (0.1-2.8)	.39	1.3 (0.3-6.7)	.74	0.4 (0.1-1.2)	.11
Sex										
Female (referent)										
Male	0.8 (0.4-1.6)	.61	0.4 (0.2-1.1)	.08	4.1 (0.8-21.6)	.10	0.5 (0.2-1.3)	.14	3.1 (1.5-6.7)	.003
Age at evaluation, y (range)	1.0 (0.9-1.1)	.85	1.1 (1.0-1.2)	.09	1.1 (1.0-1.2)	.44	1.1 (1.0-1.2)	.21	1.1 (1.02-1.2)	.01

NA indicates not applicable.

defined by the NCEP-ATPIII was 2.2% and 5%, respectively, for women and men between 18 and 40 years of age in a large study by Pannier et al in 2006.[25] Similarly, Balkau et al in 2003[26] found the prevalence to be 4% and 5.6%, respectively, for women and men between 30 and 39 years of age. Thus, adults treated for acute leukemia in childhood are at risk of developing an MS prematurely.

The MS among leukemia survivors has been previously studied. However, it is difficult to draw definitive conclusions, as the previous studies were done in small cohorts, using a highly variable definition of the MS. To our knowledge, our prospective study is one of the largest reported to date and takes advantage from using a widely recognized, reproducible definition of the MS. The only study using NCEP-ATPIII criteria comparable with ours was performed by Gurney et al[12] on a cohort of 75 adult survivors of ALL (mean age, 30.2 years). Among them, 16% met the NCEP-ATPIII MS criteria. The lower frequency of the MS we found could be explained by the younger age of our patients, the prevalence of the MS increasing with aging.[25-28]

Other studies report a frequency ranging from 5.7% in a childhood population[13] to 39% for adults treated with HSCT.[29]

Role of CNS irradiation

A recent study performed by Oeffinger et al[30] is highly informative. This study, including 118 patients treated for an ALL during childhood (median age, 23 years), evaluated the frequency of insulin resistance using homeostasis model assessment of insulin resistance (HOMA-IR) and the frequency of 6 cardiovascular risk factors composed of 4 NCEP-ATPIII criteria of the MS (except for hyperglycemia), compared with a control population. Female ALL survivors treated with CNS irradiation had a significantly higher HOMA-IR and a higher risk to have 3 or more cardiovascular risk factors than controls. Male patients (with and without CNS irradiation) were at risk of having elevated HOMA-IR. The non-CNS irradiation female patients did not differ from controls considering HOMA-IR and cardiovascular risk factors.

In our study, we were unable to demonstrate a significant effect of CNS irradiation, perhaps because of a low percentage of irradiated patients (14.7% vs 33.9% in the Oeffinger et al study[30]), which led to a lack of statistical power. This lower prevalence could reflect a more recent treatment period (year of diagnosis, 1980-2004 in our cohort vs 1970-2000), the use of CNS irradiation becoming less frequent over time.

The impact of CNS irradiation on the MS and its components was also reported by several previous studies.[10,12,16,29-33] GHD caused by CNS irradiation is considered to play a major role for the development of the MS parameters.[11,31,34] We did not demonstrate a significant link between GHD and MS, probably because of a low occurrence of GHD (9 [4.85%] patients) as side effect of CNS irradiation, the role of CNS irradiation probably being also overshadowed by the great impact of TBI.

Our results focus more on the role of TBI exposure, TBI being still the treatment of choice in pediatric conditioning regimens before stem cell transplantation.

Role of TBI exposure

To our knowledge, this large multivariate analysis is the first to demonstrate that TBI is a major risk factor for developing NCEP-ATPIII MS in adulthood (RR = 3.9, $P = .03$). TBI was found to have a dramatic impact on lipid metabolism (hypertriglyceridemia and low HDL cholesterol) and on hyperglycemia. By contrast, hypertension and increased waist circumference were similar in patients who received TBI and those who did not.

A high frequency of cardiovascular risk factors among patients who underwent HSCT has been previously reported.[29,35-37] However, the role of TBI was not specifically implicated in the genesis of the MS. Taskinen et al[37] did not demonstrate such a role for TBI, and Shalitin et al showed only an impact on glucose tolerance.[36] Neville et al found a significantly increased risk of hyperinsulinemia, impaired glucose tolerance, or diabetes mellitus associated with exposure to TBI.[38] In a large cohort of patients who underwent HSCT, Baker et al[39] showed that TBI-exposed patients were more likely to develop diabetes mellitus (OR = 3.4) but not to have hypertension. A similar association between TBI exposure and diabetes was found by Meacham et al[40] and Steffens et al.[41]

Association with hypothyroidism and hypogonadism

We found a highly significant association between MS and hypogonadism ($P = .001$). Such an association has been reported in general population,[42-45] but it has not been proved for childhood leukemia survivors.[29] However, a correlation between MS and hypogonadism had been previously found among adult stem cell transplanted patients.[46]

These findings are consistent with previous studies[17,37] in cancer survivors, but there remains little evidence to delineate the pathogenic role of hypogonadism in the development of metabolic disorders in this population.

We also found a trend for a higher risk of MS in patients with hypothyroidism, but the correlation did not reach the threshold of statistical significance. To our knowledge, such an association has not been previously reported among leukemia survivors. It might just reflect the relationship between TBI and post-transplantation hypothyroidism. However, hypothyroidism is known to be associated with lipid disturbance and higher rate of cardiovascular events in general population.[47]

Physiopathologic hypothesis

GHD has been largely implicated in the genesis of metabolic disturbances after treatment for childhood leukemia,[31,32] probably through insulin resistance and perturbations of glucose metabolism.[12,30,31,38] We did not find such an association. One bias could be the fact that we did not search systematically for GHD but only for patients who had growth delay, which probably led us to underdiagnose GHD.

Insulin resistance is usually considered to be the primary event leading to the MS.[48] More recently, some authors suggest that endothelial dysfunction could underlie the development of the MS.[49] In our population, the use of aggressive therapies, such as chemotherapy or irradiation leading to endothelial damage, could explain in part a higher occurrence of the MS. This mechanism, although it cannot be proven, has already been suggested.[13,17,32]

Another pathophysiologic mechanism has been more recently suggested: nutritional insults during a period of developmental plasticity result in a MS phenotype[50]; this concept has first been established for very low weight newborns. Such a mechanism could be implicated in cancer survivors as our patients frequently have undernutrition during the treatment. It is not clear how TBI could lead to endothelial damage or undernutrition. More findings are needed to assess the exact role of these factors.

Limits of the study

Our study has several limitations. Although insulin resistance is one of the key factors for the development of the MS, we chose not

to perform homeostasis model assessment of insulin resistance or insulin measurement. The interest of such an approach only based on clinical examination and routine biologic exploration lies in its applicability. Moreover, the validity of the clinical criteria defining the MS has been assessed in previous studies.

Despite a mean of 14.5 years of follow-up, our study population is rather young. A longer follow-up would probably be associated with an increased frequency of the MS.

In conclusion, this study underscores the need for careful follow-up of childhood leukemia survivors: a metabolic workup should be included systematically for leukemia survivors, and special attention should be paid to cardiovascular risk in TBI-exposed patients. Further studies are warranted to elucidate the pathophysiology of MS among cancer survivors and to explore the effectiveness of lifestyle intervention in reducing its risk in these patients.

Authorship

Contribution: C.O. performed research, analyzed data, and wrote the paper; G.M. designed and supervised the research, analyzed data, and wrote the manuscript; M.-C.S., B.P., M.C.M., P.A., and A.B.-L.C. analyzed data; N.S., A.C., P.B., C.C., M.P., I.T., H.C., and P.C. collected data; and all authors participated sufficiently in the work to take public responsibility for appropriate portions of the content, and gave final approval of the manuscript to be published.

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Correspondence: Claire Oudin, Department of Pediatric Hematology, Hôpital de la Timone Enfants, 264 Rue Saint Pierre 13385, Marseille, France; e-mail: oudinc@marseille.fnclcc.fr.

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