Early traits of metabolic syndrome in pediatric post-cancer survivors: outcomes in adolescents and young adults treated for childhood medulloblastoma

Fatores precoces para síndrome metabólica em sobreviventes de câncer pediátrico: resultados em adolescentes e adultos jovens tratados por meduloblastoma na infância

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ABSTRACT

Objective: To analyze traits of metabolic syndrome (MetS) in medulloblastoma survivors. **Subjects and methods:** Sixteen childhood medulloblastoma survivors aged 18.0 (4.4) years, with history of craniospinal radiation therapy (RT) were compared with nine control subjects matched by age, gender, and body mass index, according to fat distribution, metabolic and cardiovascular variables. **Results:** Medulloblastoma patients showed increases in waist circumference and its relationships (all $p < 0.05$), and HOMA1-IR ($p = 0.006$), which were modified by growth hormone (GH) secretion status. However, these increases were within normal range. **Conclusions:** Adolescent and young adult survivors of medulloblastoma showed centripetal fat deposition and decreased insulin sensitivity, associated with GH status. Pediatric brain tumor survivors following RT should be monitored for the diagnosis of MetS traits predisposing to cardiovascular disease. Arq Bras Endocrinol Metab. 2011;55(8):653-60

Keywords
Medulloblastoma/therapy; medulloblastoma/drug therapy; medulloblastoma/radiotherapy; medulloblastoma/prevention and control; cardiovascular diseases; metabolic syndrome X

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RESUMO

Objetivo: Analisar características que predispõem para síndrome metabólica (SM) em sobreviventes de meduloblastoma. **Sujeitos e métodos:** Dezesseis sobreviventes de meduloblastoma pediátrico, 18,0 (4,4) anos, história de radioterapia (RT) cranioespinhal, comparados a nove controles pareados por idade, sexo e índice de massa corporal, de acordo com distribuição de gordura, variáveis metabólicas e cardiovasculares. **Resultados:** Pacientes com meduloblastoma mostraram aumento da cintura e relações (todos $p < 0,05$) e HOMA1-IR ($p = 0,006$), modificados pela secreção do hormônio de crescimento (GH), mas dentro dos limites de normalidade. **Conclusões:** Sobreviventes adolescentes e adultos jovens de meduloblastoma apresentaram deposição centrípeta de gordura e diminuição da sensibilidade à insulina, associados ao estado do GH. Sobreviventes de tumor cerebral pediátrico que receberam RT devem ser monitorados para diagnosticar fatores para SM predispondo à doença cardiovascular. Arq Bras Endocrinol Metab. 2011;55(8):653-60

Descritores
Meduloblastoma/terapia; meduloblastoma/quimioterapia; meduloblastoma/radioterapia; medulolastoma/prevenção e controle; doenças cardiovasculares; síndrome X metabólica

INTRODUCTION

Medulloblastoma is one of the most common childhood brain malignancies, accounting for approximately 10%-20% of pediatric brain tumors. Pediatric tumor types are more sensitive to chemotherapy (CT) and to adjuvant radiation therapy (RT), compared with adults, and often require high doses of craniospinal RT, due to their propensity to disseminate within the neuraxis (1). Consequently, along with the better care provided to pediatric medulloblastoma, the spectrum of side effects is broader: RT, particularly when combined with CT, brings increased risk of severe long-term after-effects involving neurologic, cognitive, as well as endocrine and metabolic functions (2-5). In contrast to other types of tumors, especially those of the sellar region (e.g. craniopharyngioma), the resulting endocrine and metabolic derangements in medulloblastoma are exclusively secondary to therapy damage.

Post-pediatric cancer survivors, including brain tumors, may develop MetS traits due to hormonal deficiencies, particularly growth hormone (GH) deficiency, drug or RT damage, endothelial impairment, physical inactivity, and/or adipose tissue dysfunction, but this issue has not been elucidated yet (6-13). Cranial RT and its consequent hypothalamic dysfunction is one of the predisposing mechanisms involved in premature cardiovascular disease (CVD), frequently described in survivors of pediatric cancers (6). According to a statement developed by the American Heart Association along with the Council for Cardiovascular Disease in the Young, post-pediatric cancer survivors may present increase epidemiological evidence of manifesting CVD early in adult life, usually after 30 years of age (6-8).

To date, studies that focused on metabolic derangements in childhood medulloblastoma survivors are scarce because, despite the advances in therapy regimens, the relapse rate within five years after therapy withdrawal is still high. Additionally, previous reports included medulloblastoma among other types of pediatric brain tumors with cranial RT (6-8,11-12). Thus, the purpose of this study was to differentiate MetS traits in adolescents and young adult survivors of childhood medulloblastoma who were followed up in a single center. In addition, it was evaluated whether these features were modified by GH status.

METHODS

Study population

This cross-sectional study was carried out on a sample of male and female medulloblastoma survivors admitted for treatment at the Pediatric Oncology Institute, Universidade Federal de São Paulo – Unifesp/EPM, São Paulo, Brazil, from February 1990 to August 2005, and in normal healthy controls. The study was approved by the Ethical Research Committee of Unifesp/EPM, in accordance with the Declaration of Helsinki (project no. 1867/06 – Unifesp/EPM). Patients or parents, when appropriate, signed an informed consent form that allowed participation in this study.

Medulloblastoma survivors fully completed therapy regimens, which encompassed total or partial surgical resection, CT, craniospinal RT (24 Gy), and radiotherapy boost (54 Gy). CT was delineated with a combination of standard drugs comprising: carboplatin, vincristine, ifosfamide, veposide, cisplatin, cyclophosphamide, and temozolomide (2-4). Characteristics of host/disease and therapy were assessed from medical records and included patient age at diagnosis, time since therapy withdrawal, hormonal deficiencies, and therapy employed. All medulloblastoma subjects were previously evaluated in relation to GH secretion status (insulin tolerance test, ITT), and GH peak (9,10). They were then stratified into two groups for comparison: GH-deficient (*GHD)* and the Non-GHD medulloblastoma survivors, whose GH peak was, respectively, lower than or equal to 5 µg/L, or over 5 µg/L. Medulloblastoma survivors presented complete clinical remission (complete or subtotal resection, but no evidence of cerebrospinal fluid dissemination), completed the treatment protocol, and were off therapy for at least two years since diagnosis. Survivors and controls were both included in this assessment if they met the following criteria: chronological age of 12 years or older; renal, thyroid, gonadal and adrenal profiles within the normal range (spontaneous or under appropriate hormonal replacement therapy). Exclusion criteria were the following therapies and conditions: use of anorexigens, insulin-lowering medications or other drugs interfering with adiposity (e.g. metformin, sibutramine, and fluoxetine); exogenous human recombinant growth hormone (rhGH) administration two years before study enrollment; and bone marrow transplantation. The control group presented no past medical history, was matched to the medulloblastoma group based on age, gender and body mass

index (BMI), and was randomly recruited among medical students from the Unifesp/EPM.

Measurements

The following variables were transversally evaluated in both medulloblastoma survivors and controls:

Systolic and diastolic blood pressure: supine systolic and diastolic blood pressure (BP) was measured in the right arm using a manual sphygmomanometer (Tycos®), and the mean of three measurements, after a five-minute rest period, was used. Hypertension was defined according to BP cutoff points, as follows: systolic BP equal or higher than 130 mmHg, and/or diastolic BP equal or higher than 85 mmHg, or use of antihypertensive drug (patients 18 years of age or older) (14,15), or systolic and/or diastolic BP equal or higher than the 95th percentile for adolescents (16).

Anthropometric variables and body composition: weight and height were analyzed as Z-scores (Z weight and Z height, respectively) (17,18). Final adult height was defined as growth speed lower than 1.0 cm per year; bone age equal or greater than 14.5 years in girls and 16.5 in boys; being fully pubertal, as defined by Tanner stage 5 or greater, in boys; and having spontaneous menarche, in girls (19,20). Regarding BMI, which was calculated as weight divided by height in meters squared (kg/m^2), and analyzed as Z-scores, obesity was defined as BMI Z-score (Z BMI) > 2.0 standard deviation (SD) (17,18).

Total body fat (in percentage, %), lean body mass (in kg) and body water (in %) were assessed by means of electrical bioimpedance (Model 310 Biodynamics®), with patients in supine position, arms and legs away from the body. After asepsis of the skin, two electrodes were positioned distally and proximally in the right foot and hand. The mean of three measurements was used in the analysis. Total body fat above the 95th percentile was defined as obesity in patients younger than 18 years of age (21), and cutoff values based on the National Health and Evaluation Survey (NHANES) were used for patients 18 years old or older (35.2% and 30.3% for females and males, respectively) (22).

Fat distribution: the following circumferences were determined: waist circumference (WC, in cm), hip circumference (HC, in cm), and their relationships: waist-to-hip ratio, and waist-to-height ratio. WC and HC were measured according to the method described elsewhere (23). Regarding WC, the following cutoff values were considered for adults: males greater than 102 cm and females greater than 88 cm (older than 19 years of age), based on the National Cholesterol Education Program – Adult Treatment Panel III (NCEP-ATP III) (14); males 94 cm or greater and females 80 cm or greater (older than 16 years of age), according to the International Diabetes Federation (IDF) (15). Cutoff values were modified for adolescents as follows: WC equal or greater than the 90th percentile (19 years of age or older), according to NCEP-ATP III (Cook and cols. study) (24), and WC greater than the 90th percentile (16 years of age or younger) according to the IDF (25). Data from the Bogalusa Study (26) by Freedman and cols. (1999), was employed for WC percentiles. A waist-to-height ratio above 0.5 indicated visceral adiposity (27).

Metabolic profile

Lipid panel: total cholesterol, high-density lipoprotein (HDL) cholesterol, and triglycerides were determined using a colorimetric enzymatic method. Low-density lipoprotein (LDL) cholesterol was calculated by the formula described by Friedewald and cols. (1972) (28). In relation to HDL cholesterol and triglycerides, the cutoff values proposed by NCEP-ATP III and Cook and cols. (14,24), and the IDF (15,25) were considered to define dyslipidemia. As for HDL cholesterol levels, according to both criteria for adult patients (14,15), the cutoff values were below 1.0 mmol/L (males), and below 1.3 mmol/L (females). For adolescents, the cutoff values were equal or lower than 1.0 mmol/L (Cook and cols. study) (24), and lower than 1.0 mmol/L (IDF) (25), for both genders. As for triglyceride levels, according to NCEP-ATP III (14) and the IDF (15), cutoff values were equal or greater than 1.7 mmol/L for adult patients (both genders). For adolescents, the cutoff values were equal or greater than 1.2 mmol/L (Cook and cols. study) (24), and equal or greater than 1.7 mmol/L (IDF) (25), for both genders.

Glucose, insulin and insulin sensitivity: fasting glucose and insulin levels were assessed using an automated method. Altered glycemia was defined according to Genuth and cols. (29) In order to establish insulin sensitivity, glucose and insulin levels were determined to calculate the homeostatic model assessment of insulin resistance (HOMA1-IR) (30). HOMA1-IR above 2.71 (31) or above 3.16 (32) were determined as cutoff levels in adults and adolescents, respectively, to define IR. Hyperinsulinemia was defined as an insulin level above 173.6 pmol/L.

Insulin-like growth factor-1: insulin-like growth factor-1 (IGF-1) was analyzed by radioimmunoassay after organic solvent extraction and celite column partition chromatography (33,34).

Cardiovascular markers

Common carotid artery intima-media thickness: common carotid artery (CCA) intima-media thickness (IMT) was assessed by ultrasound after a mean of three measurements of the posterior wall of the bilateral common carotid, 1 cm away from the carotid bifurcation, while patients were in supine position and at rest (Toshiba Powervision® with 7-10 MHz vascular linear transducer) (33).

Two-dimensional Doppler echocardiogram: heart dimensions and variables related to systolic and diastolic function were assessed (Philips EnVisor® version C.1.3, with 2.5-3.5 MHz multifrequency transducer). Heart dimensions comprised left ventricle (LV) mass (in grams), LV mass index (LV mass corrected for body surface area, in g/m²), and left atrium (LA, in mm). LV systolic function variables included ejection fraction (EF, in %), and percent shortening (PS, in %); diastolic function variables encompassed mitral valve waves E/A ratio, mitral wave E deceleration time (msec), and myocardial performance index (MPI). EF below 55% and PS below 30% were considered as altered LV systolic function (9,33,34).

Statistical analysis

Kolmogorov-Smirnov normality test and Levene test were initially conducted to evaluate data distribution and group variances. Variables with normal distribution and equal variance were presented as means, standard deviations (SD), and 95% confidence intervals (CI). Variables that presented non-normal distribution and/or unequal variance were transformed into natural logarithm (ln) and were presented as medians and ranges (minimum - maximum). Medulloblastoma and controls were compared with respect to quantitative variables using t test for independent samples. The subpopulation of *GHD* medulloblastoma subjects was compared with the Non-GHD and normal healthy controls, using one-way analysis of variance (ANOVA) in relation to the quantitative variables described. Pairwise comparison test (Tukey's test) was carried out if ANOVA presented p < 0.05. Fisher's exact test was used to evaluate the association between prevalence of obesity (as total body fat), centripetal obesity

(circumferences and relationships), dyslipidemia (HDL cholesterol and triglycerides cutoff values), IR (as HOMA1-IR cutoff values), and disease/therapy. Alpha level was set at 0.05. Statistical analyses were performed using SPSS 13.0 (SPSS, Inc., Chicago, IL).

RESULTS

Study population

From the 81 medulloblastoma patients admitted for treatment at the IOP/GRAACC from February 1990 to August 2005, 48/81 (60%) died or abandoned therapy, and 20/81 (24.7%) were considered eligible for this study; four of them refused to participate. The study population was made up of 16 medulloblastoma survivors aged [mean (SD)] 18.0 (4.0) years, who were 11.3 (4.5) years old at the time of medulloblastoma diagnosis, 5.9 (5.3) years after therapy withdrawal. The majority was male (62.5%), 2 patients were prepubertal, and 68.7% had reached final adult height. BMI was 21.4 (4.2) kg/m² and Z BMI -0.23 (1.55). The control sample was composed of 9 subjects aged 20.0 (5.1) years, 33.3% males, all pubertal, 66.7% had reached final adult height, BMI 21.0 (2.5) kg/m² and Z BMI -0.29 (1.15) SD, as shown in table 1.

Six of the 16 (37.5%) medulloblastoma subjects were considered *GHD*; however, only 1 patient had received recombinant human GH (rhGH) for a 2-year period. In addition, 7/16 (43.7%) survivors were under levothyroxine sodium replacement therapy, with 4/16 (25%) showing spinal RT-induced primary hypothyroidism, and 3/16 (18.7%) having post-total thyroi-

Table 1. Clinical and anthropometric data of adolescent and young adult survivors of childhood medulloblastoma and normal, healthy controls matched by age, gender, and BMI

Variables	Group	
	Medulloblastoma (n = 16)	Control (n = 9)
Age at assessment (years)	18.0 (4.4)	20.0 (5.1)
Males	10/16 (62.5%)	3/9 (33.3%)
Age at medulloblastoma diagnosis (years)	11.3 (4.5)	-
Time post-treatment (years)	5.9 (5.3)	-
Final adult height	11/16 (68.7%)	6/9 (66.7%)
BMI (kg/m²)	21.4 (4.2)	21.0 (2.5)
BMI (SD)	-0.23 (1.55)	-0.29 (1.15)

Data are presented as means (SD) or frequencies. BMI: body mass index, SD: standard deviation.

dectomy secondary to thyroid nodule (2 patients diagnosed with colloid goiter and 1 patient with thyroid papillary carcinoma). Three of the 16 (18.7%) patients (all females) required hormonal replacement therapy due to therapy-induced primary gonadal failure.

Body composition, fat distribution and insulin sensitivity: WC, waist-to-hip ratio and waist-to-height ratio were statistically higher in medulloblastoma patients compared with controls (Table 2). There was a trend toward elevation of total body fat in medulloblastoma subjects; however, no subject was considered obese in BMI analysis.

Medulloblastoma patients presented higher glucose, insulin and HOMA1-IR when compared with controls (Table 3); nonetheless, no patient was glucose-intolerant or presented with hyperinsulinemia. Three of the 16 (18.7%) medulloblastoma subjects presented IR. However, there was no association between obesity, centripetal obesity, IR and disease/therapy.

Lipid panel and echocardiographic variables: HDL cholesterol and echocardiographic parameters of systolic function (EF and PS) were decreased in medulloblastoma patients compared with controls (Tables 3 and 4, respectively). There was no difference in the prevalence of dyslipidemia between medulloblastoma patients and normal healthy controls, using different criteria. No medulloblastoma patient presented alterations in EF.

Growth hormone status effect on quantitative variables: GH status modified some of the studied outcomes, in the comparison of the three groups: *GHD* (n = 6), Non-GHD medulloblastoma survivors (n = 10), and controls (n = 9), as follows: Z height, waist-to-hip and waist-to-height ratios, glucose, HOMA1-IR, and EF (ANOVA, $p < 0.05$). After a multiple comparison test, Z height and EF were decreased in *GHD*, compared with Non-GHD medulloblastoma survivors. Waist-to-hip and waist-to-height ratios, glucose, and HOMA1-IR were increased in *GHD* medulloblastoma subjects, compared with controls (Tukey's test, all tests $p < 0.05$).

Table 2. Blood pressure, anthropometric, body composition and fat distribution variables in adolescent and young adult survivors of medulloblastoma, compared with normal healthy controls (* $p < 0.05$)

Variables	Medulloblastoma (n = 16)	Control (n = 9)	[95% CI of the difference] p value
Systolic BP (mmHg)	108.4 (14.4)	106.7 (8.7)	[-9.2; 12.7] 0.752
Diastolic BP (mmHg)	61.6 (56.6 - 80)	60.3 (58.6 – 76.7)	- 0.634
Weight Z-score (SD)	-0.86 (1.42)	-0.44 (1.10)	[-1.56; 0.70] 0.449
Height Z-score (SD)	-1.28 (1.19)	-0.87 (1.34)	[-1.49; 0.66] 0.432
Total body fat (%)	22.3 (10.8)	14.9 (9.0)	[-1.3; 16.2] 0.093
Lean body mass (kg)	41.6 (13.2)	39.8 (12.3)	[-9.3; 12.9] 0.742
Body water (%)	70.9 (6.3)	69.2 (2.5)	[-2.8; 6.3] 0.441
WC (cm)	76.8 (10.1)	67.9 (5.6)	[1.3; 16.6] 0.024*
HC (cm)	90.3 (10.1)	92.9 (10.2)	[-11.3; 6.2] 0.547
Waist-to-hip ratio	0.85 (0.06)	0.74 (0.07)	[0.05; 0.16] 0.001*
Waist-to-height ratio	0.50 (0.40 - 0.60)	0.40 (0.40 - 0.50)	- 0.018*

Values are expressed as means (SD) [95% CI of the difference] or medians (range); CI: confidence interval; SD: standard deviation; BP: blood pressure; WC: waist circumference; HC: hip circumference.

Table 3. Metabolic and vascular variables in adolescent and young adult survivors of medulloblastoma, compared with normal healthy controls (* $p < 0.05$)

Variables	Medulloblastoma (n = 16)	Control (n = 9)	[95% CI of the difference] t test p value
Total cholesterol (mmol/L)	4.4 (0.9)	4.0 (1.6)	[-0.7; 1.4] 0.465
LDL cholesterol (mmol/L)	2.6 (0.7)	2.3 (0.6)	[-0.3; 0.8] 0.357
HDL cholesterol (mmol/L)	1.3 (0.4)	1.6 (0.2)	[-0.5; 0.0] 0.053
Triglycerides (mmol/L)	1.0 (0.7)	0.9 (0.5)	[-0.5; 0.6] 0.874
IGF-1 (nmol/L)	34.8 (17.0)	32.3 (8.6)	[-10.1; 15.2] 0.682
Glucose (mmol/L)	4.9 (0.5)	4.5 (0.4)	[0.0; 0.8] 0.045*
Insulin (pmol/L)	40.3 (13.9 – 121.5)	17.4 (13.9 – 27.0)	- 0.002*
HOMA1-IR	1.15 (0.40 – 3.80)	0.40 (0.40 – 0.90)	- 0.006*
Right CCA IMT (mm)	0.65 (0.09)	0.61 (0.05)	[-0.02; 0.12] 0.191
Left CCA IMT (mm)	0.65 (0.51 – 0.84)	0.63 (0.51 – 0.65)	- 0.426

Values are expressed as means (SD) [95% CI of the difference] or medians (range); CI: confidence interval; SD: standard deviation; LDL: low density lipoprotein, HDL: high density lipoprotein; IGF-1: insulin-like growth factor-1; HOMA1-IR: homeostasis model assessment-insulin resistance; CCA: common carotid artery; IMT: intima-media thickness.

Table 4. Echocardiographic variables in adolescent and young adult survivors of medulloblastoma, compared with normal healthy controls (* p < 0.05)

Variables	Medulloblastoma (n = 16)	Control (n = 9)	[95% CI of the difference] p value in t test
LV mass (g)	85.1 (28.1)	91.5 (19.9)	[-28.4; 15.6] 0.553
LV mass index (g/m²)	55.7 (12.7)	59.8 (8.1)	[-13.9; 5.7] 0.394
LA (mm)	28.6 (3.2)	30.2 (2.6)	[-4.2; 1.0] 0.216
Ejection fraction (%)	67.8 (4.2)	72.3 (6.4)	[-8.9; -0.1] 0.043*
Percent shortening (%)	34.0 (4.3)	37.7 (3.8)	[-7.1; -0.02] 0.049*
Mitral valve waves E:A ratio	1.76 (0.28)	1.70 (0.31)	[-0.20; 0.32] 0.626
Mitral wave E deceleration time (msec)	180.9 (37.4)	197.2 (25.4)	[-46.9; 14.2] 0.279
Myocardial performance index	44.0 (20.0 – 87.0)	39.0 (30.0 – 53.0)	- 0.556

Values are expressed as means (SD) [95% CI of the difference] or medians (range); CI: confidence interval; SD: standard deviation; LV: left ventricle; LA: left atrium.

DISCUSSION

This study investigated whether adolescent and young adult survivors of medulloblastoma already present MetS traits. The major finding of this study was that some MetS traits, such as centripetal fat deposition, altered lipid profile and decreased insulin sensitivity, were detected, at a young age, in childhood medulloblastoma survivors with history of craniospinal RT, compared with normal healthy controls, even though within normal limits so far. Additionally, GH status influenced fat distribution variables, and insulin sensitivity was also observed.

Adiposity, possibly by means of hyperinsulinism and IGF-1, has a role in promoting carcinogenesis and, in its turn, carcinogenesis could also contribute to the development of MetS in survivors of various malignancies (6,35). In this study, body composition was evaluated by electrical bioimpedance, and fat distribution by circumferences and their relationships, which are not the gold standard methods to date. Nevertheless, total body fat showed a trend toward increase, and WC ratios were all increased (particularly in the *GHD* subpopulation) in medulloblastoma patients, which is in accordance with previous studies (11), even though this

increase was within normal limits. Waist-to-height ratio is the index that better reflects centripetal deposition of fat (27) and has a strong correlation with visceral fat evaluated by magnetic resonance imaging, which is the gold standard (36). However, we must emphasize that waist-to-height ratio should be carefully interpreted in this sample, since *GHD* medulloblastoma subjects presented decreased Z height, as a consequence of spinal RT. Hypothalamic lesion (and GH deficiency) secondary to craniospinal RT could possibly be one of the main causes of alterations in body fat compartments and decreased height in patients treated for medulloblastoma (3,4,6,8). That is the reason why current regimens are proposing low doses of craniospinal RT (18 Gy) to treat nondisseminated medulloblastoma, despite the aggressiveness of the disease, in order to diminish endocrine after-effects (37,38). These kind of studies are scarce and analyze medulloblastoma together with other malignancies. Notwithstanding, the risk of central obesity in survivors of childhood cancer, including acute lymphocytic leukemia, craniopharyngioma, following bone marrow transplantation (BMT), and brain tumors with cranial RT history, has already been described and concurs with the present study (6-13).

IR is the factor that links all other MetS criteria, together with endothelial dysfunction (6,8,36). In this study, medulloblastoma survivors showed increased insulin secretion, decreased insulin sensitivity, and an unfavorable lipid profile. However, to date, these variations are within normal values. Hyperinsulinemia and an adverse lipid profile have been described as an effect of therapy in patients treated for various types of cancer with adjuvant RT, and after BMT (6,8-11,39). In addition, GH status was associated with insulin sensitivity in this sample.

In relation to CCA IMT, which reflects premature asymptomatic atherosclerosis, there was no difference between medulloblastoma patients and controls in this study, and no association with GH status. On the other hand, previous studies have described increased IMT in brain tumor survivors and non-oncologic *GHD* children and adolescents (11,33). Furthermore, it is known that IMT is positively correlated with RT dosage, and negatively correlated with IGF-1 levels which, in turn, reflect GH secretion status (6,33,34,40). In the present study, the young age of the sample might explain the lack of difference between the groups, ever since all medulloblastoma patients received high doses of cranial RT (54 Gy). Echocardiographic evaluation showed de-

creased systolic function in medulloblastoma subjects, and an effect of GH, but without clinical relevance. GH is important for cardiac function and contractility, and CT (particularly with anthracyclines) may impair this function (8,9,12).

The population studied in the present evaluation was made up of only 16 medulloblastoma survivors, who were off therapy for at least 2 years from diagnosis, all treated with CT and craniospinal RT. The small size of the sample is due to the fact that medulloblastoma is an extremely aggressive, highly recurrent tumor, limiting the population to be studied (1-5). Nonetheless, they were compared with matched controls, and some differences related to fat distribution and metabolic derangements were evidenced. Although it was not the aim of this study, some other factors, rather than chronological age, could explain the absence of some abnormalities in this subgroup of patients, such as shorter post-treatment interval, overprotection, extreme parental health care, and medical support (6).

In conclusion, patients treated for childhood medulloblastoma at a mean age of 18 years, 5.9 years off therapy presented centripetal adiposity, and decreased insulin sensitivity, all outcomes modified by GH deficiency. No signs of asymptomatic atherosclerosis were detected; however, there were alterations in systolic function variables. Medulloblastoma survivors should be followed up for early diagnosis of metabolic abnormalities, in a way to prioritize interventions and reduce the occurrence of CVD between 30-40 years of age, in this population.

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