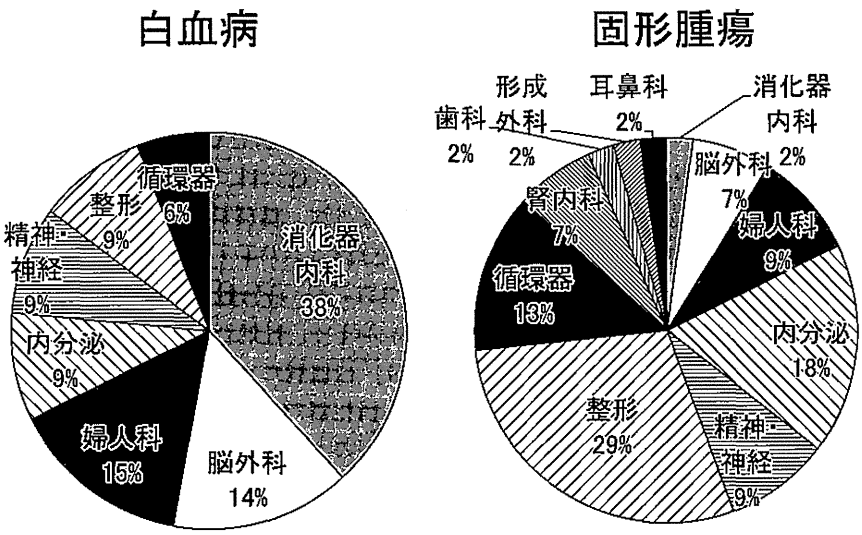

図2　併診科の内訳

の仲間との交流が少ない場合，社会性の発達へ影響する．学生の間は，先生や友人が助けてくれることも多く，顕著にならずに経過していても，社会人になるときにより明らかになる．

当科には，15年ほど前に小児がん経験者の会ができ，現在まで活発な活動を続けている．仲間の存在は非常に大きく，苦しんでいるのは自分だけでないことがわかり，自分自身が明るく前向きになった．というような意見を聞く．診療で足りない部分を補ってくれる貴重な存在である．

小児がん経験者の中には，他人になかなか相談できずに悩んでいる人も数多いが，他にも同じような悩みを持ちながら歩んでいる仲間がいることや，小児がん経験者の会の情報を与えることで，安心や希望が出てくるのを痛感している．

V　考　案

小児がんが治らなかった時代に，がん治療による後遺症のことを心配していた臨床医はいないだろう．当然のことながら，まず目の前にある小児がんを治すのが先決であり，後遺症のことを案ずる余地はなかった．この40年の間に，70%以上の小児がんが治癒するようになり，小児がん治療後，時を経るほどに晩期合併症の発症頻度が増えることがわかってきた[1]．この事実は，小児がん経験者本人のみならず，小児がん治療医にとっても大変な衝撃である．できることならば，小児がんが治癒したことで，病院と縁を切ってしまいたい．という思いは，本人・家族のみならず，医療者にもあったと考える．

小児がん治癒後の長い人生において，長期にフォローアップをしながら，本人をサポートしていくこと，また以前の治療で起こった合併症を明らかにしながら，次の治療へ反映させていくことは非常に重要なことであることが，我が国の小児がん治療医全体に認識されるようになって，それほど長い年月が経過したわけではないだろう．長期FUのシステムを確立させるのが急務であることは，治療医のだれもが認識していることであるが，忙しい小児がん治療の傍らで，FUの体制までも確立させるには多大な労力を要し，簡単なことではないのが現状である．

当科では，以前より血液腫瘍外来の時間枠の中でLTFUを行っていた．しかしながら，血液腫瘍外来では，治療中や治療終了後間もない子ども達の診療に多くの時間を費やすので，LTFUに十分な時間をとるために，別の曜日にLTFU外来枠を設けた．一人一人の表情を見ながら，話をしながら，まだまだ手探りで行っている外来である．治療終了後長期が経過した人が増え，二次がんがますます増加してくることが考えられる．LTFUの中でがん検診を行うのは難しいが，個々の原発がんの種類や治療内容に応じたスクリーニングと，地域のがん検診を必ず受診すること，子宮頸がんワクチン接種のすすめ，など，フォローアップ手帳を活用しながら行っている．本年，小児がんが「がん対策基本法」に盛り込まれ，今後のLTFUがより円滑となるようなシステムの確立を期待したい．

また，LTFUにおいては，小児がん経験者への指導・教育が大切であり，次のポイントをおさえたい．

1. 病気の理解をしっかりと
   正しい病名・病状・治療を理解して，体調の自己管理・起こりうる合併症とその予防を行う．
2. よき理解者・相談相手を確保する
   ・家族，友人

・闘病体験のある仲間
・医療関係者（医師，看護師，MSW，心理士など）

なかでも，闘病体験のある仲間との出会いは大きく，お互いに励ましあいながら成長する姿を目の当たりにしてきた．今後もLTFUを通じて，支援していきたいと考える．

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Original Article

Adipocytokines in childhood cancer survivors and correlation with metabolic syndrome components

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Abstract ***Background***: Although there are several studies on the prevalence of metabolic syndrome (MetS) in childhood cancer survivors (CCS), the association between MetS components and serum adipocytokine level has not been elucidated.

Methods: The charts of 49 patients (27 male, 22 female) who had attended the CCS clinic of the Department of Pediatrics, Kyoto University Hospital, between April 2009 and March 2010 were retrospectively reviewed. Median age was 10.7 years, and the median interval since the completion of chemotherapy was 5.1 years. The diagnosis of MetS was made based on the Japanese criteria for either children or adults.

Results: Three (6.1%) of 49 patients fulfilled the criteria for MetS, and 28 (57.1%) had at least one component of MetS. High leptin level was seen in 18 patients (36.7%), and low total adiponectin level was seen in 20 (40.8%). The number of patients with high leptin was correlated with body mass index z-score (>2.0), abdominal circumference/height (≥0.5), diastolic blood pressure and fasting blood sugar. The number of patients with low total adiponectin was correlated with systolic blood pressure and triglyceride. When the patients were divided into three groups based on the number of positive MetS components (0, 1 and 2–4), leptin and adiponectin tended to be higher and lower in the third group, respectively.

Conclusions: Adipocytokines may play a role in the pathogenesis of MetS occurring in CCS. It is recommended that adipocytokines be evaluated together with MetS components at the CCS follow-up clinics.

Key words adipocytokine, cancer survivor, child, late effects, metabolic syndrome.

The prognosis for childhood cancer has improved in recent decades, with 5 year survival rates reaching approximately 80%.[1–3] In contrast, this improvement in the survival rate in childhood cancer has caused a number of treatment-related complications, that is, late effects, among childhood cancer survivors (CCS). Obesity is a well-recognized late effect,[4,5] and is sometimes accompanied by obesity-associated metabolic abnormalities known as metabolic syndrome (MetS).[6–11] There has been increasing evidence that MetS or its components are more prevalent in adult survivors of childhood cancer.[6,7,9,10] Cranial or total body radiation, growth hormone deficiency, and impaired morbidity are thought to be associated with the occurrence of MetS.[6–10]

Previous studies have indicated a link between obesity or MetS and various adipocytokines such as leptin and adiponectin in obese children and adolescents.[11–13] Leptin acts to reduce bodyweight by decreasing food intake and increasing energy expenditure.[11] Adiponectin is closely linked to adiposity and insulin resistance through the modulation of glucose and lipid metabolism.[12,13] In healthy children, it is reported that serum leptin level is positively associated with the occurrence of MetS, whereas serum adiponectin level is negatively associated with the occurrence of MetS.[10–14] There are several reports on the relationship between obesity or MetS and adipocytokines in CCS,[15–17] but the relationship has not been fully elucidated, especially in young CCS. Moreover, reports measuring high-molecular-weight adiponectin in CCS are sparse. Therefore, the purpose of this study was to clarify the serum levels of leptin and adiponectin, including high-molecular-weight adiponectin, in relation to the prevalence of MetS components in CCS.

Methods

Patients

Forty-nine patients (27 male, 22 female) visiting the follow-up clinic for CCS at the Department of Pediatrics, Kyoto University Hospital, from April 2009 to March 2010, were enrolled. They were diagnosed as having various types of cancer at <16 years of age between 1983 and 2007. The conditions for eligibility for the present study were: (i) remission; (ii) freedom from any type of cancer treatment for the previous 3 years; (iii) present age >6 years; and (iv) availability of complete clinical data. The median age at diagnosis was 5.1 years (range, 0.2–14.2 years), the median present age was 10.7 years (range, 6.0–25.3 years), and

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the median interval since the completion of chemotherapy was 5.1 years (range, 3.0–14.6 years).

Procedure

We retrospectively reviewed the charts of 49 patients to determine their diagnoses and the treatment modalities used (i.e. chemotherapy, radiation therapy, and hematopoietic stem cell transplantation, HSCT). The patient characteristics are summarized in Table 1. The treatment modalities used for the 49 patients included chemotherapy ($n = 49$; 100%), HSCT ($n = 16$; 32.7%), total body irradiation ($n = 9$; 18.4%) and cranial irradiation ($n = 2$; 4.1%). Patients with chronic myeloid leukemia were not treated with tyrosine kinase inhibitors. It is of note that there were no patients with brain tumors, because those patients were mainly treated in the neurosurgery department. The data collected for each patient included height, weight, waist circumference, systolic and diastolic blood pressures (SBP and DBP), high-density lipoprotein cholesterol (HDL-C), triglycerides (TG), and fasting blood sugar (FBS). The serum levels of leptin, total adiponectin (T-adiponectin) and high-molecular-weight adiponectin (H-adiponectin) were measured using serum samples stored at −70°C until use. The serum levels of leptin and adiponectin were assayed by radioimmunoassay and enzyme-linked immunosorbent assay, respectively (Mitsubishi Petrochemical, Tokyo, Japan). Because reference values for adiponectins based on a large survey of Japanese children are not available, we used the data obtained by Yoshinaga *et al.* as the reference data for children under 15 years of age.[14] In adolescents and adults, we used the data obtained by Matsubara *et al.* for leptin[18] and by Ehara *et al.* for adiponectin as the reference.[19]

Definition of MetS and MetS components

The body mass index (BMI) z-scores were calculated using the least mean squares method based on the reference data.[20] MetS for children was defined according to the criteria established by the Health, Labour and Welfare Ministry of Japan in 2006.[21] The criteria are applicable to children between the ages of 6 and 15 years, and include: (i) abdominal obesity (i.e. waist circumference ≥80 cm for junior high school students, ≥75 cm for elementary school students, and/or waist/height ratio ≥0.5); (ii) SBP ≥125 mmHg and/or DBP ≥70 mmHg; (iii) TG ≥120 mg/dL and/or HDL-C <40 mg/dL; and (iv) FBS ≥100 mg/dL. We adapted these criteria to high school students (i.e. children up to 18 years old) because there are no MetS criteria specific to high school students. In four patients >18 years old, MetS was diagnosed based on the Japanese criteria for adults.[22] These criteria include: (i) abdominal obesity (i.e. waist circumference ≥85 cm for men and ≥90 cm for women); (ii) SBP ≥130 mmHg and/or DBP ≥85 mmHg; (iii) TG ≥150 mg/dL and/or HDL-C <40 mg/dL; and (iv) FBS ≥110 mg/dL. In both sets of criteria, a diagnosis of MetS was made when patients fulfilled condition (i), abdominal obesity (required) and at least two of conditions (ii)–(iv).

Table 1 Patient characteristics and treatment modalities

Total (n)	49
Gender (n), M : F	27/22
Age at diagnosis (years), median (range)	5.1 (0.2–14.2)
Years since completion of treatment, median (range)	5.1 (3.0–14.6)
Present age (years), median (range)	10.7 (6.0–25.3)
Diagnosis	
ALL	23
AML	10
CML	2
Lymphoma†	3
Solid tumor‡	11
Treatment	
Chemotherapy only	31
Chemotherapy + Cranial radiation	2
Chemotherapy + HSCT	7
Chemotherapy + TBI + HSCT	9

†Burkitt lymphoma, $n = 1$; T-lymphoma, $n = 1$; non-Hodgkin lymphoma, $n = 1$. ‡Retinoblastoma, $n = 3$; osteosarcoma, $n = 2$; neuroblastoma, $n = 2$; Wilm's tumor, $n = 2$; hepatoblastoma, $n = 1$; germinoma, $n = 1$. HSCT: hematopoietic stem cell transplantation; TBI, total body irradiation.

Statistical Analysis

Fisher's exact test was used to compare categorical variables including gender and the prevalence of MetS components between two groups, and Cochran–Armitage test was used for three groups. Mann–Whitney test and Kruskal–Wallis test were applied to assess the differences of continuous variables between two and between three groups, respectively. All statistical analysis was carried out using Stat Mate (version III; Atoms, Tokyo, Japan). $P < 0.05$ was considered statistically significant.

Results

Prevalence of MetS and components of MetS

Three (6.1%) out of 49 patients were found to have MetS (Table 2). With regard to the components of MetS, 18 (36.7%) and 10 (20.4%) patients had at least one and more than two components, respectively. Among abnormal MetS components, the prevalence of hypertriglyceridemia was most common, followed by hypertension (Table 2). Notably, only three patients (10.7%) had abdominal obesity. The number of MetS components in each patient group are listed in Table 2.

Demographic features and MetS components vs adipocytokine level

We classified the patients into two groups each with regard to leptin level (normal or high) and T-adiponectin level (normal or low), based on the reference values given here. Table 3 lists the number of patients belonging to each group versus present age, gender, treatment modalities, and MetS components. In the high leptin group, the number of patients with female gender, BMI z-score (≥2.0), abdominal circumference/height (≥0.5), high DBP, and high FBS was significantly higher than in the control group. In the low T-adiponectin group, the number of patients with high SBP and high TG was significantly higher than in the control group. When the analysis was done for the acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML)

Table 2 Prevalence and components of MetS vs disease group

MetS	Disease group					Total, *n* (%)†
	ALL	AML	CML	Lymphoma	Solid tumor	
Presence of MetS						
Yes	2	1	0	0	0	3 (6.1)
No	21	9	2	3	11	46 (93.9)
No. positive MetS components‡						
0	8	5	1	3	4	21 (42.9)
1	9	3	1	0	5	18 (36.7)
2	4	1	0	0	2	7 (14.3)
3	2	0	0	0	0	2 (4.1)
4	0	1	0	0	0	1 (2.0)
MetS components						
Abdominal obesity	2	1	0	0	0	3 (10.7)†
Hypertriglyceridemia	10	3	0	0	3	16 (57.1)
Low HDL-C	3	0	0	0	0	3 (10.7)
Hypertension	10	3	1	0	1	15 (53.6)
High fasting blood sugar	1	0	0	0	4	5 (17.9)

†Total number of patients with positive MetS components (28 patients) used as the denominator. ‡Abdominal obesity was classified as one component of MetS. ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; CML, chronic myeloid leukemia; HDL-C, high-density lipoprotein cholesterol; MetS, metabolic syndrome.

patient groups, however, a statistically significant difference was found only for abdominal circumference/height with regard to leptin level (Table 4).

Demographic features and adipocytokine level vs no. MetS components

Next, we classified the patients into three groups according to the number of positive MetS components: 0, 1, and 2–4 (Table 5). Although an increase in leptin and in the ratio of leptin to T-adiponectin, and a decrease in T-adiponectin and H-adiponectin and the ratio of H-adiponectin to T-adiponectin were observed, the differences were not statistically significant.

Discussion

Although previous studies of CCS noted a prevalence of MetS of 8–33%,[6,7,9,10] we found MetS in only three patients (6.1%). There are several possible explanations for the discrepancy. First, the history of cranial radiation was closely associated with the occurrence of obesity and MetS in CCS,[6,8] but only two patients (4.1%) in the present study had received cranial radiation. Second, the time since the completion of cancer treatment was short in the present study compared with previous studies.[6,7,9,10] In other words, the present cohort mainly consisted of young survivors of childhood cancer. Finally, the present diagnostic criteria for MetS were specific to Japan, especially in that the component of abdominal obesity is included as a requisite for the diagnosis of MetS.[21] It should be noted, however, that the present results are in line with the report by Ishida *et al.* on Japanese CCS.[23]

As for the components of MetS, the number of patients with hypertriglyceridemia, which was the most prevalent of MetS components, was 16 (57.1%), whereas only three patients (10.7%) had low HDL-C. The cut-off point for dyslipidemia in

Table 3 Total subject characteristics and MetS components vs adipocytokine level

Subject characteristics	Adipocytokines					
	Leptin			T-Adiponectin		
	Normal (*n* = 31)	High (*n* = 18)	*P*	Normal (*n* = 29)	Low (*n* = 20)	*P*
Present age (years), median (range)	10.4 (5.9–19.7)	15.1 (6.9–25.3)	0.12†	10.4 (7.5–25.3)	13.8 (5.9–19.6)	0.17†
Gender (M : F)	21:10	6:12	<0.05‡	15:14	12:8	0.77‡
Treatment (chemotherapy only : others)	21:10	10:8	0.54‡	20:9	11:9	0.38‡
BMI z-score (>2.0)	0 (0)	3 (16.7)	<0.05‡	1 (3.4)	2 (10.0)	0.56‡
Positive MetS components, no. patients (%)						
Abdominal circumference/height	0 (0)	3 (16.7)	<0.05‡	0 (0)	3 (15.0)	0.062‡
SBP	4 (12.9)	5 (27.8)	0.26‡	2 (6.8)	7 (35.0)	<0.05‡
DBP	5 (16.1)	9 (50.0)	<0.05‡	5 (17.2)	9 (45.0)	0.054‡
Fasting blood sugar	1 (3.2)	5 (27.8)	<0.05‡	4 (13.8)	2 (10.0)	1.00‡
Triglyceride	9 (29.0)	8 (44.4)	0.35‡	6 (20.7)	11 (55.0)	<0.05‡
HDL-C	3 (9.1)	0 (0)	0.29‡	1 (3.4)	2 (10.0)	0.56‡

†Mann–Whitney *U*-test; ‡Fisher's exact test. BMI, body mass index; DBP, diastolic blood pressure; HDL-C, high-density lipoprotein cholesterol; MetS, metabolic syndrome; SBP, systolic blood pressure.

Table 4 ALL and AML subject characteristics and MetS components vs adipocytokine level

Subject characteristics	Adipocytokines					
	Leptin			T-Adiponectin		
	Normal (n = 21)	High (n = 12)	P	Normal (n = 16)	Low (n = 17)	P
Present age (years) median (range)	10.0 (6.0–19.7)	16.9 (6.9–18.3)	0.053†	9.9 (7.5–17.8)	14.5 (6.0–19.7)	0.14†
Gender (M : F)	15:6	4:8	0.066‡	9:7	10:7	1.00‡
Treatment (chemotherapy only : others)	11:10	7:5	1.00‡	8:8	10:7	0.73‡
BMI z-score (> 2.0)	0 (0)	1 (8.3)	0.36‡	0 (0)	1 (5.9)	1.00‡
Positive MetS components, no. patients (%)						
Abdominal circumference/height	0 (0)	3 (25.0)	<0.05‡	1 (6.3)	2 (11.8)	1.00‡
SBP	4 (19.0)	4 (33.3)	0.42‡	2 (12.5)	6 (35.3)	0.22‡
DBP	5 (23.8)	6 (50.0)	0.15‡	4 (25.0)	7 (41.2)	0.46‡
Fasting blood sugar	0 (0)	1 (8.3)	0.36‡	0 (0)	1 (5.9)	1.00‡
Triglyceride	7 (33.3)	6 (50.0)	0.47‡	4 (25.0)	9 (52.9)	0.16‡
HDL-C	3 (14.3)	0 (0)	0.28‡	1 (6.3)	2 (11.8)	1.00‡

†Mann–Whitney U-test; ‡Fisher's exact test. ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; DBP, diastolic blood pressure; HDL-C, high-density lipoprotein cholesterol; MetS, metabolic syndrome; SBP, systolic blood pressure.

the diagnosis of MetS in Japanese children is based on the 90th percentile for TG and the 5th percentile for HDL-C among the general population of Japanese children.[24] The high prevalence of hypertriglyceridemia found in the present study was consistent with a previous report on CCS with sarcoma (17/32; 53%).[7] In other reports, however, the prevalence was found to be around 20%, but low HDL-C was more prevalent (12–64%).[6,8,25] Previous studies indicated that the occurrence of dyslipidemia was closely associated with abdominal obesity. It is remarkable that the number of CCS having both abdominal obesity and dyslipidemia was only three (6.1%) in the present study. Although the reasons for the disparity are uncertain at present, this finding may indicate the need for regular blood examinations even in non-obese CCS.

Adipocytokines such as leptin or adiponectin play an important role in the occurrence of obesity and MetS in healthy children[11–14] and in adults.[26] There are only a few studies, however, that have examined the role of adipocytokines in obesity or MetS in CCS. In ALL survivors, leptin level was strongly associated with BMI-standard deviation scores (SDS) only in male survivors, regardless of cranial radiation.[27] In contrast, Karaman *et al.* reported that serum leptin level had a significant correlation with BMI-SDS in ALL female survivors receiving cranial radiation.[16] Decreased T-adiponectin level was noted in ALL survivors with HSCT compared with those without HSCT.[28] Moschovi *et al.* measured plasma adipocytokines serially during therapy in ALL patients, although their study cohort did not include CCS. They found that: (i) low T-adiponectin and high leptin levels were found at diagnosis; (ii) during the maintenance phase, T-adiponectin increased and leptin decreased significantly; and (iii) toward the end of therapy, T-adiponectin level remained lower than that of controls.[29] Tonorezos *et al.* reported recently that insulin resistance as measured by elevated homeostasis model of assessment–insulin resistance (HOMA-IR) was associated with a high leptin : T-adiponectin ratio among ALL survivors.[17] The present findings are in line with these previous reports with regard to the total patient group, but when the samples were restricted to ALL and AML patients, the difference became smaller. The tendency for both H-adiponectin level and the ratio of H-adiponectin to T-adiponectin to decrease as the number of MetS components increases, as far as we know, is a new finding.

There are several limitations to the present study. First, because the present cohort consisted of CCS of heterogeneous cancers that were treated using diverse treatment modalities, it was difficult to determine the influence of each treatment. Second, we did not have reference values for several adiponectins examined in the present study. Therefore, we used previous data

Table 5 Subject characteristics vs no. MetS components, median (range)

Subject characteristics	No. MetS components			P
	0	1	2–4	
No. patients	21	18	10	
Present age (years)	10.7 (5–25)†	10.7 (8–20)	11.2 (7–18)	0.87†
Gender (M : F)	11:10	12:6	4:6	0.84‡
Leptin (ng/mL)	3.6 (1.1–24.8)	4.6 (1.7–19.5)	6.2 (1.9–17.6)	0.82†
Total adiponectin (mg/mL)	8.5 (3.6–14.5)	7.1 (3.9–16.6)	6.5 (2.9–11.1)	0.31†
High-molecular-weight adiponectin (mg/mL)	3.7 (1.4–8.5)	3.1 (1.3–7.8)	2.6 (0.6-6.0)	0.15†
Leptin/total adiponectin	0.49 (0.09-3.97)	0.78 (0.11-4.51)	0.77 (0.17-4.97)	0.26†
High-molecular-weight/total adiponectin	0.47 (0.29-0.74)	0.41 (0.27-0.56)	0.38 (0.12-0.62)	0.068†

†Kruskal–Wallis test; ‡Cochran–Armitage test. MetS, metabolic syndrome.

for healthy children from the literature as the reference values,[14,18] although the number of samples collected in these studies is thought to be insufficient. Finally, the period since the completion of treatment was short compared with those in previous studies.[16,17] This may have led to the small number of patients with MetS. Further follow up of the subject group is necessary.

Conclusion

There was a high prevalence of abnormal adipocytokine levels including H-adiponectin in CCS. High leptin and low T- and H-adiponectin levels may be associated in part with the occurrence of specific MetS components. Further study is warranted to delineate the pathogenesis of the changes in adipocytokines and MetS components and the relationship between them.

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