



Early Endocrine and Metabolic Complications in Childhood Cancer Survivors—Experience from a Tertiary Care Pediatric Oncology Center in South India

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Abstract



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Keywords

- ▶ survivors
- ▶ childhood cancer
- ▶ endocrine
- ▶ metabolic syndrome
- ▶ complications

Background Endocrine abnormalities and metabolic complications remain one of the common late effects after cancer therapy in children. Data on the incidence and pattern of complications would help to guide appropriate monitoring and treatment of childhood cancer survivors.

Methods, Aims, and Objectives Purpose of study is to determine endocrine and metabolic effects in childhood cancer survivors including both hematological malignancies and solid tumors due to cancer per se and treatment-related, including different chemotherapeutic agents and radiotherapy.

Results Among 97 participants, 84 children (84.5%) had at least one endocrine or metabolic complication; 41 children (42.3%) had more than two endocrine/metabolic complications. Common endocrine complications included precocious puberty (6.2%), short stature (6.2%), and hypothyroidism (5.1%). Among metabolic complications, dyslipidemia was the highest with an incidence of 68%, followed by fasting hyperinsulinism (32%), diastolic hypertension (18.6%), systolic hypertension (11.3%), obesity (8.8%), and metabolic syndrome (8.2%) and impaired fasting glucose (4.1%).

Among endocrine complications, there was a significant increase in incidence of hypothyroidism among children receiving radiotherapy (odds ratio [OR]: 7.13, 95% confidence interval [CI]: 1.1–46.2), and among metabolic complications, a significant increase in incidence of metabolic syndrome in children treated with L-asparaginase compared with those not treated with L-asparaginase was observed (OR: 5.61, 95% CI: 1.07–29.5). There was no significant difference between incidence of observed

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endocrine and metabolic complications based on type of tumor, gender, and puberty status of study participants.

Conclusion This study suggests that there is significant incidence of endocrine and metabolic complications in childhood cancer survivors, hence timely and appropriate recognition of these complications by appropriate screening recommendations and pursuing further endocrine evaluation rationally is needed.

Introduction

Survival in childhood cancer has significantly increased above 80% in developed nations of the world. As the survivors of childhood cancer continue to increase, there is an exponential need for evidence-based surveillance of the long-term effects of cancer therapy. Endocrine and metabolic complications are more prevalent in childhood cancer survivors (CCSs). Bhatia et al reported in their recent review that the most common adverse effects in individuals who survived childhood cancer are endocrine disorders, such as hypothyroidism (HT) or growth hormone deficiency (GHD; 44%).¹ There is a need for clinicians and patients to have heightened awareness of these complications to diagnose them promptly and early intervention is very important.

Methods

This hospital-based descriptive study was conducted in the Department of Pediatric Hemato-oncology at our tertiary care institution from August 2015 to August 2017. Children between the ages of 2 and 18 years who have completed at least 1 year after cancer treatment (chemotherapy/radiotherapy/surgery/combination of these) were included in the study. Written consent was obtained from the parents.

After enrolment, anthropometric parameters (height, weight, body mass index [BMI], pubertal evaluation, systolic and diastolic blood pressure). All anthropometric measurements were measured (as per-existing protocols) in triplicate and averaged. For all anthropometric data, World Health Organization (WHO) 2006 charts were used for children aged 2 to 5 years and revised Indian Academy of Pediatrics 2015 charts were used for children aged 5 to 18 years of age.² Height, weight, and BMI were converted to standard deviation scores for ease of analysis across different ages in the study population. For pubertal stage assessment, Tanner's sexual maturity rating was used.^{3,4} For further statistical analysis, all children with Tanner stage 1 were grouped as prepubertal and children with Tanner staging 2 to Tanner staging 5 were grouped as pubertal. Ethical approval was obtained from the institutional ethics committee (Ref. no. CSP-MED/15/AUG/24/46).

As per study protocol, 8 mL blood was drawn for lipid profile (total cholesterol, triglycerides, high-density cholesterol, and low-density cholesterol), fasting glucose, fasting insulin, thyroid-stimulating hormone (TSH), and FreeT4 (FT4). NHLBI (National Heart, Lung, and Blood Institute)

cutoffs were used for lipid profile.⁵ For defining metabolic syndrome, WHO definition was used.⁶ Fasting hyperinsulinism was defined by fasting insulin level >15 mIU/mL for prepubertal children or >26 mIU/mL for pubertal children.⁷ Insulin resistance was analyzed by homeostasis model assessment of insulin resistance (HOMA-IR) using the formula $[FBG \text{ (mg/dL)} \times FI \text{ (}\mu\text{U/mL)}] / 405$.⁸ Fasting insulin, TSH, and FT4 were analyzed by chemiluminescence immunoassay. Fasting glucose was done by the glucose oxidase peroxidase method. Lipid profile was analyzed using cholesterol oxidase and enzymatic end-point analysis.

All descriptive data were expressed as mean \pm standard deviation. Qualitative data were compared by the Chi-square test. Comparison of means was done using Student's *t*-test. Statistical significance was taken as $p < 0.05$. All statistical analyses were performed using SPSS version 16.

Results

Clinical and biochemical data are described in **Table 1**. The mean age of study population is 9.4 ± 4.8 years; 64% in the study were boys. Fifty-six children (57.7%) had hematolymphoid malignancies, and 41 children (42.3%) had solid tumors. In this cohort, 52 children were prepubertal (53.6%) and 45 children (46.4%) were in pubertal stage of Tanner 2 and above. **Fig. 1** represents the distribution of malignancies observed in the study population.

Among treatment options, chemotherapy alone was received by 54 children (55.6%), 2 children received radiotherapy alone (2.1%), surgical approach alone was needed in 4 children (4.1%). Combined therapies like chemotherapy + radiation, chemotherapy + surgery, and chemotherapy + radiotherapy + surgery were received by 12 (12.4%), 20 (20.6%), and 5 (5.2%), respectively.

Among the cancer survivors, 84 children (84.5%) had at least one endocrine or metabolic complication and 41 children (42.3%) had more than two endocrine or metabolic complications. Among the complications, HT was observed in 5 (5.1%), short stature in 6 (6.2%), and precocious puberty in 6 children (6.2%). Overt HT was observed in one child with short stature. Among metabolic complications, 8 children (8.8%) had obesity, 11 children (11.3%) had systolic hypertension, 18 children (18.6%) had diastolic hypertension, 4 children (4.1%) had impaired fasting glucose, 31 children (32%) had fasting hyperinsulinism, 66 children (68%) had dyslipidemia, and 8 children (8.2%) had metabolic syndrome (**Table 2**). Among children less than 5 years of age,

Table 1 Clinical and biochemical characteristics of study population

Clinical characteristics	Hematological malignancies (n = 56)	Solid tumors (n = 41)	p-Value
Male:female (n)	36:20	26:15	p = 0.930
Age (years)	10.2 ± 5.1	8.3 ± 4.1	p = 0.055
Prepubertal:pubertal (n)	26:30	26:15	p = 0.097
Weight SDS	0.03 ± 1.6	-0.08 ± 1.3	p = 0.704
Height SDS	-0.07 ± 1.6	-0.13 ± 1.6	p = 0.86
BMI SDS	0.1 ± 1.4	-0.1 ± 1.2	p = 0.47
Systolic blood pressure	101.3 ± 15.1	98.3 ± 14.6	p = 0.33
Diastolic blood pressure	70.3 ± 11.0	68.6 ± 12.4	p = 0.49
Fasting blood sugar	85.6 ± 12.4	84.8 ± 12.6	p = 0.75
Fasting insulin	18.4 ± 20.6	15.5 ± 15.0	p = 0.45
HbA1C	5.1 ± 0.4	4.98 ± 0.5	p = 0.14
HOMA-IR	4.2 ± 5.2	3.3 ± 3.5	p = 0.31
Total cholesterol	152.3 ± 25.7	150.8 ± 22.1	p = 0.76
Triglycerides	105.5 ± 45.4	100.7 ± 39.7	p = 0.59
HDL	58.1 ± 12.9	57.4 ± 11.9	p = 0.79
LDL	85.7 ± 21.7	83.8 ± 19.1	p = 0.49
TSH	2.64 ± 2.05	2.3 ± 1.1	p = 0.35
FT4	1.3 ± 0.3	1.3 ± 0.4	p = 0.75

Abbreviations: BMI, body mass index; HDL, high-density lipoprotein; LDL, low-density lipoprotein; SDS, standard deviation score; TSH, thyroid-stimulating hormone.

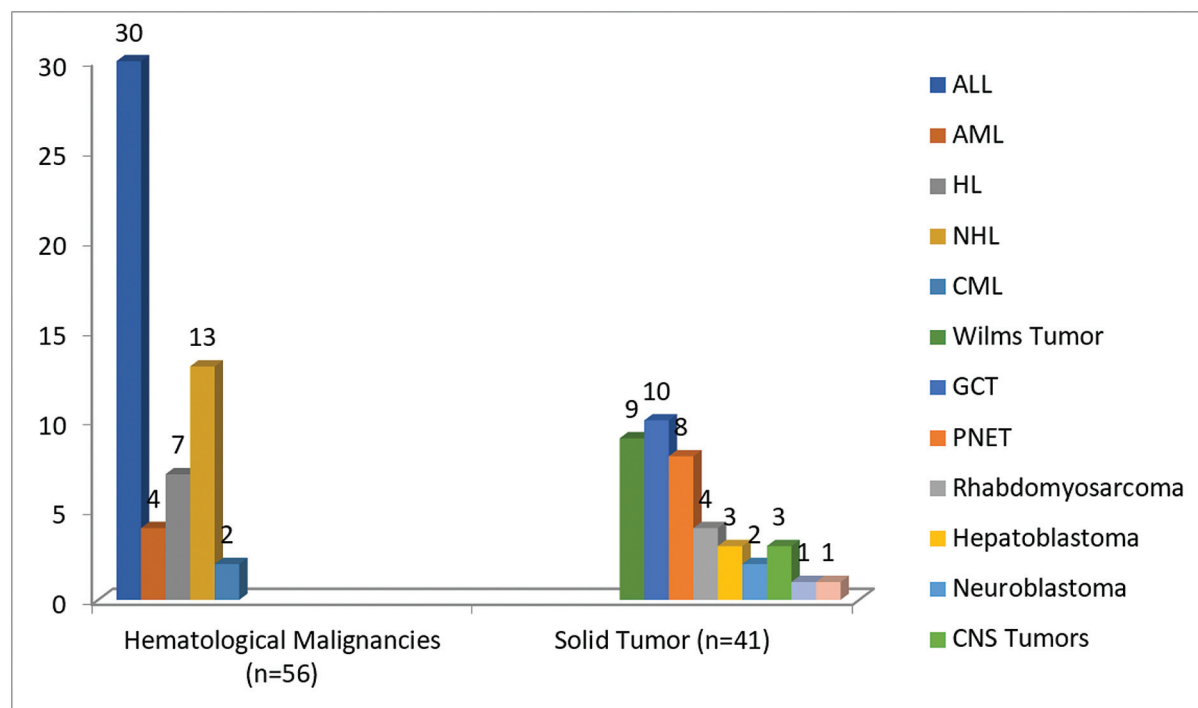


Fig. 1 Common malignancies observed in the study population. ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; CML, chronic myeloid leukemia; GCT, germ cell tumor; HL, Hodgkin's lymphoma; NHL, non-Hodgkin's lymphoma; PNET, primitive neuroectodermal tumor.

Table 2 Endocrine and metabolic complications among childhood cancer survivors according to tumor type

Complications, n (%)		Hematological malignancies (n = 56), n (%)	Solid tumors (n = 41), n (%)	p-Value
Hypothyroidism 5 (5.1%)	Subclinical	0	1	0.413
	Overt	2	1	
	Central	0	1	
Short stature 6 (6.2%)		2	4	0.212
Precocious puberty 6 (6.2%)		5	1	0.190
Nutritional status	Moderate acute malnutrition, 3 (3.1%)	1 (1.8%)	2 (4.9%)	0.928
	Severe acute malnutrition, 2 (2.1%)	1 (1.8%)	1 (2.4%)	
	Overweight, 14 (14.4%)	8 (14.3%)	6 (14.6%)	
	Obesity, 8 (8.8%)	5 (8.9%)	3 (7.3%)	
Systolic hypertension, 11 (11.3%)		6 (10.7%)	5 (12.2%)	0.820
Diastolic hypertension, 18 (18.6%)		10 (18%)	8 (19.5%)	0.836
Impaired fasting glucose, 4 (4.1%)		3 (5.4%)	1 (2.4%)	0.475
Fasting hyperinsulinism, 31 (32%)		19 (33.9%)	12 (29.3%)	0.627
Dyslipidemia, 66 (68%)		37 (66.1%)	29 (70.7%)	0.627
Metabolic syndrome, 8 (8.2%)		7 (12.5%)	1 (2.4%)	0.75

moderate acute malnutrition was observed in 3 children (3.1%) and severe acute malnutrition was observed in 2 children (2.1%).

As shown in **Table 3**, HT was frequently observed in children receiving radiotherapy (3 children out of 19 children receiving radiotherapy, odds ratio [OR]: 7.13, 95% confidence interval: 1.1–46.2, $p = 0.019$).

Metabolic syndrome was frequently observed in children treated with L-asparaginase compared with those not treated with L-asparaginase (16.2 vs. 3.3% respectively, OR: 5.61, 95% confidence interval: 1.07–29.5, $p = 0.025$) and details are shown in **Table 4**.

No significant differences were observed with the incidence of endocrine and metabolic complications based on the type of tumor, gender, and pubertal status (**Tables 2–4**).

Discussion

Nearly two-thirds of all CCSs will suffer some late effect, and the endocrine system is commonly involved.^{9,10} Wheeler et al in their systematic review of the risk of radiation-related central endocrine effects including 4,629 publications, with a total of 570 patients, showed 18 cohorts reporting GHD, 7 reporting for central HT, and 6 reported adrenocorticotropic hormone deficiency.¹¹

These are further influenced by the age at which treatment was initiated, the length of time since treatment, and gender.^{12,13} HT, pituitary disorders, and pubertal disorders are the most common endocrine sequelae observed in several studies.^{14–16} Our study shows that endocrine and metabolic complications are observed as early as 1 year of survival.

In the study by Sánchez González et al¹⁴ among 55 CCSs enrolled with minimum of 2-year survival period, primary hypogonadism was the common endocrine sequelae, followed by pituitary and thyroid disorders. Similar observations were seen in studies by Shalitin et al.¹⁵ However, in our study, obesity, short stature, precocious puberty, and HT were observed to be the commonest endocrine abnormalities and dyslipidemias, the commonest observed metabolic abnormality. This could be due to the differences in the study population enrolled and the type of therapies received.

Survivors who have received 20-Gy cranio-spinal radiotherapy had the highest risk for developing HT.^{16,17} The Childhood Cancer Survivor Study cohort had observed a cumulative incidence of HT of 1.6%.¹⁷ In our study, HT was observed in 15.8% of patients receiving radiotherapy.

The risks of obesity and diabetes mellitus are significantly higher in CCS than in their siblings.¹³ Metabolic syndrome has been shown to affect a sizeable proportion of survivors (31.8%) and at a higher rate than in the general population of adults younger than 40 years of age (18.3%).^{17,18} Alkylating agents, glucocorticoids, and irradiation are observed to be the most common causes of metabolic complications. However, in our study, metabolic syndrome was observed to be more frequent in children receiving L-asparaginase therapy (16.2%). To the best of our knowledge, no such associations have been shown for L-asparaginase therapy. Steroids being the backbone of acute lymphoblastic leukemia management could be a confounder for this observation.

Ours was a single-center study with a small sample size. Long-term follow-up is needed to confirm the study findings. Nevertheless, our study adds up to the observation of

Table 3 Presence of endocrine complications according to treatment, chemotherapeutic agents received, gender, and pubertal status

		Short stature	Hypothyroidism	Precocious puberty	Obesity
Treatment	Chemotherapy (n = 91)	6 (6.6%), p = 0.516	5 (5.5%), p = 0.95	6 (6.6%), p = 0.516	8 (8.8%), p = 0.45
	Radiotherapy (n = 19)	2 (10.5%), p = 0.381	3 (15.8%), p = 0.019 ^a	2 (10.5%), p = 0.381	1 (5.3%), p = 0.51
Chemotherapy	Steroids (n = 45)	2 (4.4%), p = 0.51	2 (4.4%), p = 0.53	4 (8.9%), p = 0.304	5 (11.1%), p = 0.56
	L-asparaginase (n = 37)	2 (5.4%), p = 0.802	1 (2.7%), p = 0.73	3 (8.1%), p = 0.54	5 (13.5%), p = 0.22
	Steroids + L-asparaginase (n = 36)	1 (2.8%), p = 0.2	1 (2.8%), p = 0.75	2 (5.6%), p = 0.84	6 (16.7%)
		8			p = 0.12
	Steroids + anthracyclines (n = 42)	2 (4.8%), p = 0.61	1 (2.4%), p = 0.64	4 (9.5%), p = 0.23	5 (12%), p = 0.62
	Steroids + Alk. agents (n = 44)	2 (4.5%), p = 0.54	1 (2.3%), p = 0.59	4 (9.1%), p = 0.28	5 (11.4%), p = 0.59
	Steroids + methotrexate (n = 8)	2 (5.3%), p = 0.76	0, p = 0.33	4 (10.5%), p = 0.15	5 (13.2%), p = 0.62
	Anthracyclines + alk. agents (n = 64)	3 (4.7%), p = 0.39	2 (3.1%), p = 0.67	4 (6.2%), p = 0.97	5 (7.8%), p = 0.75
	Platins + anthracyclines (n = 4)	0, p = 0.6	0, p = 0.6	0, p = 0.6	1 (25%), p = 0.69
	Platins + alk. agents (n = 13)	1 (7.7%), p = 0.81	2 (15.4%), p = 0.05	1 (7.7%), p = 0.81	2 (15.4%), p = 0.61
Gender	Male (n = 62)	p = 0.46	p = 0.5	p = 0.89	p = 0.67
	Female (n = 35)	3 (4.8%) 3 (8.6%)	3 (4.8%) 2 (5.7%)	4 (6.5%) 2 (5.7%)	6 (9.7%) 2 (5.7%)
SMR	Prepubertal (n = 52)	p = 0.06	p = 0.53	p = 0.304	p = 0.58
	Pubertal (n = 45)	1 (1.9%) 5 (11.1%)	3 (5.8%) 2 (4.4%)	2 (3.8%) 4 (8.9%)	3 (5.8%) 5 (11.1%)

^aLevel of significance $p < 0.05$.

endocrine and metabolic complications in CCS in as early as 1 year following cancer treatment.

Conclusion

Significant endocrine and metabolic complications are observed among CCSs, as early as 1 year from the completion of treatment. Timely and appropriate recognition of these complication is necessary for optimal health care of these children.

Ethical Approval

Ethical approval was obtained from the institutional research ethics committee of Sri Ramachandra Institute

of Higher Education and Research (Ref. no. CSP-MED/15/AUG/24/46).

Author's Contribution

S.T.T., D.S., D.J., and D.L.J. worked on the data analysis and wrote the initial draft; D.L.J., D.S., and L.M. contributed to the manuscript data and editing the draft; D.J. revised it for clinical content, and final revision for intellectual content by D.J. and J.X.S. All the other authors were involved in the management of the child. All authors read and approved the final manuscript.

Funding

The study conforms to the Declaration of Helsinki.

Table 4 Presence of metabolic complications according to treatment, chemotherapeutic agents received, gender, and pubertal status

Treatment	Impaired fasting glucose	Hyperinsulinism	Hypertension	Dyslipidemia	Metabolic syndrome
Chemotherapy (n = 91)	4 (4.4%), p = 0.6	5 (5.5%), p = 0.95	28 (30.8%), p = 0.33	62 (68.1%), p = 0.94	8 (8.8%), p = 0.45
Radiotherapy (n = 19)	0, p = 0.31	3 (15.8%), p = 0.031	9 (47.4%), p = 0.11	14 (73.7%), p = 0.56	2 (10.5%), p = 0.69
Steroids (n = 45)	2 (4.4%), p = 0.88	16 (35.6%), p = 0.48	9 (20%), p = 0.92	28 (62.2%), p = 0.25	5 (11.1%), p = 0.34
L-asparaginase (n = 37)	2 (5.4%), p = 0.62	15 (40.5%), p = 0.16	9 (24.3%), p = 0.36	24 (64.9%), p = 0.6	6 (16.2%), p = 0.025 ^a
Steroids + L-asparaginase (n = 36)	1 (2.8%), p = 0.61	14 (38.9%), p = 0.26	8 (22.2%), p = 0.62	24 (66.7%), p = 0.82	5 (13.9%), p = 0.12
Steroids + anthracyclines (n = 42)	2 (4.8%), p = 0.78	16 (38.1%), p = 0.26	9 (21.4%), p = 0.69	25 (59.5%), p = 0.12	5 (11.9%), p = 0.25
Steroids + Alk.	2	16 (36.4%)	9 (20.5%)	27	5
Agents (n = 44)	(4.5%), p = 0.85	p = 0.4	p = 0.85	(61.4%) p = 0.2	(11.4%) p = 0.31
Steroids + methotrexate (n = 38)	2 (5.3%), p = 0.65	15 (35.9%), p = 0.2	9 (23.7%), p = 0.42	25 (65.8%), p = 0.7	5 (13.2%), p = 0.16
Anthracyclines + al. k. agents (n = 64)	2 (3.1%), p = 0.49	19 (29.7%), p = 0.5	11 (17.2%), p = 0.41	43 (67.2%), p = 0.8	7 (10.9%), p = 0.18
Platins + anthracyclines (n = 4)	0, p = 0.67	0, p = 0.16	0, p = 0.31	2 (50%), p = 0.43	0, p = 0.54
Platins + alk. agents (n = 13)	0, p = 0.42	4 (30.8%), p = 0.921	3 (23.1%), p = 0.73	10 (76.9%), p = 0.46	0, p = 0.24
Gender					
Male (N = 62)	p = 0.64	p = 0.59	p = 0.54	p = 0.84	p = 0.5
Female (N = 35)	3 (4.8%)	21 (33.9%)	11 (17.7%)	46 (74.2%)	6 (9.7%)
	1 (2.9%)	10 (28.6%)	8 (22.9%)	20 (57.1%)	2 (5.7%)
SMR					
Prepubertal (n = 52)	p = 0.88	p = 0.48	p = 0.54	p = 0.25	p = 0.09
Pubertal (n = 45)	2 (3.8%)	15 (28.8%)	9 (17.3%)	38 (73.1%)	2 (3.8%)
	2 (4.4%)	37 (71.2%)	10 (22.2%)	28 (62.2%)	6 (13.3%)

^aLevel of significance p < 0.05.

Conflict of Interest

None declared.

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