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Faculty of Medicine

Premature ovarian insufficiency in women after treatment for childhood cancer is a risk factor for metabolic syndrome

Axel Netterlid[a] MD, Helena Mörse[b] MD PhD, Aleksander Giwercman[c] MD PhD, Emir Henic[c] MD PhD, Eva-Marie Erfurth[d] MD PhD
Maria Elfving[e] MD PhD

[a] Lund University, Helsingborg Hospital, Department of Pediatrics, Pediatric Endocrinology Lund, Sweden [b] Lund University, Skåne University Hospital, Department of Pediatrics, Pediatric Oncology and Hematology, Lund, Sweden, [c] Lund University, Skåne University Hospital, Department of Reproductive Medicine, Malmö, Sweden [d] Lund University, Skåne University Hospital, Department of Endocrinology, Lund, Sweden, [e] Lund University, Skåne University Hospital, Department of Pediatrics, Pediatric Endocrinology, Lund, Sweden

Aims

We aimed to study the prevalence of metabolic syndrome (MetS) in women treated for cancer during childhood and explore if female hypogonadism was a risk factor for MetS.

Objective

Childhood cancer survivors (CCS) are at risk of several late effects, among them MetS. Another late side effect of cancer treatment is gonadal dysfunction, which in female CSS may result in premature ovarian insufficiency (POI), i e ovarian insufficiency below age 40 years. Since menopause and POI in the general population is associated with impaired cardio-metabolic health we tested the hypothesis that ovarian dysfunction in female CCS would increase the risk of metabolic syndrome.

Methods

The study included 167 female CCS, mean age 34.3 (range 19.3-57.8) years in the South region of Sweden, identified from the Swedish Cancer Registry and 164 controls, mean age 35.0 (range 19.3-58.0) years. The female CCS were diagnosed at mean age 8.9 (0.1-17.9) years with a mean follow up time of 25.4 (11.6-41.3) years. The distribution of childhood cancer diagnoses was representative when compared with cancer diagnoses in Sweden for females < 19 years. The prevalence of MetS and odds ratio (OR) for MetS after different treatments and ovarian dysfunction was studied. In the POI group those with hypothalamic/pituitary dysfunction were not included.

Results

For background data see Tables 1 and 2a + b.
POI was diagnosed in 13% (22/167) ($p<0.01$) among CCS compared to 0/164 among controls.
MetS was present in 14% (24/167) among all CCS ($p<0.001$), in 18% (4/22) of those with POI ($p<0.05$), compared to 2% (4/164) among controls.
OR for MetS after different treatments and in the presence of POI was compared to controls, see Table 3.

Conclusion

The incidence of MetS was higher in females treated for childhood cancer compared to controls. In addition to established risk factors as cranial irradiation and chemotherapy the presence of POI also significantly increased the risk of developing MetS.

Table 1. Study population - background data.

	All CCS n=167	CCS with POI n=22	Controls n=164
Age at examination (yr)	34.3 (19.3–57.8)	38.9 (21.9–55.5)	35.0 (19.3–58.0)
Age at diagnosis (yr)	8.9 (0.1–17.9)	10.9 (0.4–17.9)	n.a.
Time since diagnosis (yr)	25.4 (11.6–41.3)	28.0 (12.1–39.4)	n.a.
Height (cm)	164.3 (143.0–181.5)**	163.1 (143.0–181.5) *	168.5 (150.0–186.4)
Weight (kg)	67.7 (41.0–125.0)	61.8 (43.5–92.4)	66.8 (46.6–107.2)
Body mass index (kg/m²)	25.1 (16–44)**	23.4 (18–34)	23.5 (18–35)
Smoking	15 (10%)	2 (9%)	14 (9%)
POI n (%)	**22 (13%)****	22 (100%)	0
Hypothalamic-pituitary ovarian insufficiency n (%)	5 (3%)	0	0
HRT n (%)	20 (12%) **	15 (68%) **	0
Insulin treatment n (%)	1 (<1%)	1 (5%)	0
Metformin/oral antidiabetics n (%)	0	0	0
Hypertensive treatment n (%)	13 (8%)	3 (14%)	3 (2%)
Lipid lowering treatment n (%)	3 (2%)	2 (9%)	0
Growth hormone treatment n (%)	26 (16%)	4 (18%)	0
Thyroxine treatment n (%)	33 (20%)	9 (41%)	10 (6%)
Cortisone treatment n (%)	8 (5%)	1 (5%)	0
Metabolic syndrome n (%)	**24 (14%) ****	**4 (18%) ***	4 (2%)

Data presented as mean, range and percent. CCS; childhood cancer survivor, POI; premature ovarian insufficiency, n.a.; not applicable, yr;years, HRT; hormone replacement therapy * $p < 0.05$, **$p < 0.01$ (Fisher´s exact test)

Tables 2 a + b. Study population, diagnoses and treatment.

Diagnoses	CCS n (%) 167 (100)
Leukemia	51 (30)
Brain tumor	39 (23)
Lymphoma	21 (13)
Sarcoma	18 (11)
Wilms tumor	19 (11)
Ovarian tumor	11 (7)
Other	8 (5)

Type of treatment	All CCS n = 167 (%)	POI n = 22 (%)
Radiotherapy	87 (52)	17 (77)
Cranial irradiation	53 (32)	7 (23)
Abdominal irradiation	34 (20)	16 (73)
Both cranial and abdominal irradiation	16 (10)	7 (32)
TBI	7 (4)	5 (23)
Chemotherapy	126 (75)	20 (91)
Alkylating agent	81 (49)	14 (64)
HSCT	11 (7)	7 (23)
Only surgery	19 (11)	0

TBI; total body irradiation, HSCT; hematopoietic stem cell transplantation

Table 3. Odds ratio (OR) for MetS.

	Odds ratio (OR)	CI upper	CI lower	p-value
CCSF n= 167	**6.71**	2.28	19.81	0.001
POI including hypothalamic-pituitary ovarian insufficiency n= 27	**9.09**	2.27	36.44	0.002
POI n=22	**8.89**	2.05	38.62	0.004
All irradiation n=87	**8.33**	2.67	25.99	0.000
Cranial irradiation n=53	**9.30**	2.78	31.12	0.000
Abdominal irradiation n=34	**5.33**	1.26	22.50	0.023
Alkylating agents n=81	**9.09**	2.91	28.41	0.000
All cytotoxic n=126	**7.10**	2.35	21.46	0.001
Cranial irradiation and no alkylating agents n=27	**6.96**	1.63	29.75	0.009
Only operation n=19	4.71	0.80	27.61	0.086

CI; confidence interval

The IDF (International Diabetes Federation) **definition MetS:**
Central obesity (waist circumference > 80cm) **AND any two** of the following (or treatment for):
Triglycerides: > 150 mg/dL (1.7 mmol/L),
HDL cholesterol: < 50 mg/dL (1.29 mmol/L),
Blood pressure (BP): systolic > 130 or diastolic BP >85 mmHg
Fasting plasma glucose (FPG): >100 mg/dL (5.6 mmol/L)

References:
1. Cardiovascular Risk in Women With Premature Ovarian Insufficiency Compared to Premenopausal Women at Middle Age. NM Daan et al. JCEM 2016 Sep;101(9):3306-15.
2. Metabolic syndrome as cardiovascular risk factor in childhood cancer survivors. VG Pluimakers et al. Crit Rev Oncol Hematol 2019 Jan;133:129-141.

E-mail: axel.netterlid@med.lu.se

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Axel Netterlid
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