

Research Article

Hyperparathyroidism in Survivors of Childhood Malignancy after Total Body Irradiation

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Abstract

Objective: The risk of developing hyperparathyroidism (HPT) in adults after radiation exposure is higher than that of the general population. Extensive follow up guidelines of United Kingdom Children's Cancer Study group (UKCCSG) or Scottish intercollegiate guidelines network (SIGN) do not recommend monitoring serum calcium or parathyroid hormone in patients treated for childhood malignancies.

The aim of this study was to examine the occurrence of HPT in a cohort of survivors of childhood malignancy attending a late effects clinic after their treatment for haematological and non-haematological malignancies that included previous irradiation

Design and methods: Study was performed in 105 patients attending a late effects clinic. These patients had received different modalities of treatment including surgery, chemotherapy, radiotherapy and bone marrow transplant for haematological and non-haematological malignancies in their childhood with. All patients had evaluation for thyroid and parathyroid disease with a clinical examination and biochemical investigations. Patients with hyperparathyroidism were treated with parathyroidectomy in the absence of thyroid disease and positive localization on imaging. This resulted in normalization of serum calcium.

Conclusion: This data suggests that there is a significant risk of hyperparathyroidism in young females with haematological malignancies who received total body irradiation as a single fraction for bone marrow transplant.

ABBREVIATIONS

HPT: Hyperparathyroidism; P-HPT: Primary Hyperparathyroidism; UKCCSG: *United Kingdom Children's Cancer Study Group*; CCLG: *Children's Cancer and Leukemia Group*; SIGN: *Scottish Intercollegiate Guidelines Network*; TBI: *Total Body Irradiation*

INTRODUCTION

Primary hyperparathyroidism (p-HPT) is a common endocrine disease with an annual incidence of about 20 cases per 100000. In menopausal women, the prevalence is up to 3.4%. It is asymptomatic in 75 to 80 percent of cases. Most cases 85-95% are sporadic and caused by single adenoma, only 5-10% are multi glandular. Five per cent of the cases are inherited in the setting of syndromes like multiple endocrine neoplasia (MEN) type 1 or 2, familial hyperparathyroidism and primary hyperparathyroidism jaw tumor syndrome. Less than 1% is caused by parathyroid carcinoma [1]. In children and young adults p-HPT is a rare endocrine disease and these patients tend to have inherited hyperparathyroidism with multiple gland involvement [2,3]. The association of hyperparathyroidism (HPT)

and radiation exposure was first suggested in 1975 in a case report by Rosen et al., [4]. Several retrospective reports further confirmed the connection between HPT and radiation exposure [5], and laboratory experiments have documented an increased incidence of parathyroid adenomas in irradiated animals [6]. Despite evidence that supports this association, radiation-associated HPT is not nearly as widely known or well studied as the relationship between thyroid disease and head and neck radiation. Even the extensive follow up guidelines of Children's Cancer and Leukaemia Group (CCLG) or Scottish intercollegiate guidelines network (SIGN) do not recommend monitoring serum calcium or parathyroid hormone in patients treated for childhood malignancies. The risk of developing hyperparathyroidism after radiation exposure has been estimated to be 2.9 times that of the general population [7]. Some groups published much higher incidence. In 1984 Nader et al concluded that patients who received neck radiation therapy for malignant disease are not at an increased risk for the

Development of hyperparathyroidism in the first two decades following treatment but should continue to be screened for this development in subsequent decades [8]. The aim of

this study was to examine the occurrence of HPT in a cohort of survivors of childhood malignancy attending a late effects clinic after their treatment for haematological and non-haematological malignancy that also included previous irradiation

MATERIALS AND METHODS

Data were obtained retrospectively from 105 consecutive survivors of childhood haematological and non-haematological malignancies attending a late effects clinic between 2006 and 2008. These patients had received different modalities of treatment that included surgery, chemotherapy, radiotherapy and bone marrow transplant. Patients were transferred for long-term follow up to this clinic once they had been disease free for at least 2 years after treatment. Data recorded included age at diagnosis and treatment and the types of treatment. Details regarding the nature of radiation therapy included the total dose and whether given in single or as multiple fractions were obtained from the oncology Department of Royal Marsden Hospital. All patients had evaluation for thyroid and parathyroid disease with clinical examination, thyroid function tests, parathyroid hormone (PTH), and serum calcium (Ca⁺) measurements. Patients were considered to have HPT if their serum Ca⁺ and PTH levels were above the normal reference range. 25 hydroxy vitamin D (25(OH) D) was only measured in patients who had HPT and replaced if patients had vitamin D deficiency. Parathyroid imaging and bone mineral density (BMD) measurements were also performed on these patients. The imaging included a high-resolution ultrasound scan of the neck and a sestamibi scan. Patients with HPT were referred for surgery if there was localization of parathyroid adenoma on one of the imaging modalities. Serum calcium and PTH levels were monitored and patients were seen for follow-up at 4 weeks, 2 months and at 6 months after parathyroidectomy. Data were analyzed using SPSS v15. Results are reported as mean + SD unless stated otherwise.

RESULTS

105 cases attending late effects clinic were evaluated. There were 56 male and 49 female patients. All patients had normal renal functions. 70% had haematological malignancies either leukaemia or lymphoma with females comprising 51% and males 49%. 30% had non- haematological malignancies. This group had 52% female and 48% males. The number of specific tumours in non- haematological malignancies is documented in (Table 1). 61 patients (58%) had radiation exposure as a part of their treatment either on its own or in combination with surgery and chemotherapy. 32 of the total 61 patients (52%) who received radiotherapy had neck exposure secondary to TBI and craniospinal irradiation. Hyperparathyroidism was identified in 11 of the 105 patients (10.4%) of the survivors of childhood malignancies. All the patients diagnosed with hyperparathyroidism had received radiation.

Male Versus Female

Data is presented in (Table 2). The average age at evaluation was 25.6 + 5.5 years for males and 25.7 + 5.0 years for females (p = 0.96). The average age at treatment for malignancy was 10.14 + 7.4 years for males and 8.3 + 5.5 years for females (p = 0.92). Serum free thyroxine (FT4) and thyroid stimulating hormone

Table 1: Distribution of childhood Malignancies.

Hematological	Numbers	Non-Hematological	Numbers
Total	74	Total	31
Acute lymphoblastic leukemia	45	Ewing's Sarcoma	4
Acute Myeloid leukemia	10	Medulloblastoma	5
Hodgkins and non Hodgkins lymphomas	19	Astrocytoma	5
		Histiocytosis	3
		Rhabdomyosarcoma	2
		Optic nerve glioma	2
		Wilms tumor	2
		Craniopharyngioma	5
		Germ cell tumor	3

Table 2: Males and females.

Variable	Male	Female
Number	56	49
Age at study (Years)	25.6 + 5.5	25.7 + 5
Age at diagnosis (Years)	10.14 + 7.4	8.3 + 5.5
Height (cm)	149.7 + 57.6	144.3 + 49.7
Weight (kg)	65.1 + 22.9	62.0 + 13.5*
Total body irradiation (Number)	9 (16%)	14 (28%)
Dose of Total body irradiation (GY)	10.5	10.5
Free T4 (12-24 pmol/l)	15.1 + 7.7	14.9 + 4.2
TSH (0.4-4.0 mu/l).	1.63 + 1.63	2.33 + 2.3
Sr calcium (2.17-2.47mmol/l)	2.24 + 0.07	2.46 + 0.13*
PTH (1.1 - 6.9 pmol/l)	3.94 + 1.6	5.65 + 3.17*

* P = <0.05 Free T4: Free Thyroxine; TSH: Thyroid Stimulating Hormone; PTH: Parathyroid Hormone

(TSH) were not statistically different in two sexes. Serum Ca⁺ and serum PTH concentrations were significantly higher in females as compared to males.

Haematological versus non- haematological malignancies

Data are presented in (Table 3). Mean age at follow up was not statistically different in the two groups. Age at treatment was significantly lower in haematological malignancies (9.03 + 4.8) as compared to non-haematological malignancies (10.03 + 9.5). Radiotherapy was used in 53% of cases with haematological malignancies as a part of combination treatment and in 71% of cases with non-haematological malignancies. 23 out of the 74 patients (31%) with haematological malignancies

had total body irradiation (TBI) as a conditioning for bone marrow transplant. This group comprised of 14 female and 9 male patients. 15 patients had TBI as single fraction 10.5Gy and 8 had fractionated TBI 14.4Gy in 8 fractions. All patients in non-haematological malignancies group had fractionated radiotherapy with a mean dose of 31.8 + 40.6Gy. (p=0.000).

Free T4 and TSH were statistically not different in haematological and non-haematological group (p=0.78, p = 0.14 respectively) but serum Ca⁺ was significantly higher in the haematological malignancy group (2.37 + 0.15 mmol/l versus 2.28 + 0.10 mmol/l, p= <0.05) when compared to non-haematological malignancy group whereas PTH was not different (p=0.36).

TBI versus no TBI

Data is presented in (Table 4). The average age at the time of follow up was not statistically different between the two sexes. Females who received TBI had significantly higher Ca⁺ (2.56 + 0.09 versus 2.21 + 0.07) and higher PTH (8.8 + 2.94 versus 3.11 + 0.45) as compared to the males who had also received TBI.

The results overall showed a significant gender effect with females exhibiting higher levels of Ca⁺ than males (p=<0.001) irrespective of TBI.

Fifteen percent of the patients (11 out of 74) had HPT were in the haematological malignancy group. These were all females and had received TBI in a single fraction for bone marrow transplant conditioning. None of the patient in non-haematological group had HPT.

The average age at exposure to radiation was 10.14 + 7.4 years for males and 8.3 + 5.5 years for females (p =0.92). The average time since exposure to radiation and diagnosis of HPT was 15.3 + 3.8 years for men and 16.2 + 3.2 years for females. Seven of

Table 4: TBI and no TBI groups.

Variable	TBI		No TBI	
	Male	Female	Male	Female
Sex				
Number	9	14	47	35
Age at study (Years)	26.1 ± 4.5	25.2 ± 4.06	25.5 ± 5.7	25.9 ± 5.4
Sr calcium (2.17 - 2.47 mmol/l)	2.23 ± 0.08	2.53 ± 0.10*	2.24 ± 0.07	2.42 ± 0.10**
PTH (1.1 - 6.9 pmol/l)	1.14 ± 1.87	5.91 ± 3.96*	1.16 ± 2.07	2.27 ± 2.97**
P= <0.05				
*Significant differences between the groups				
**Significant differences between the sexes				
TBI= Total Body Irradiation				
PTH = Parathyroid Hormone				

the patients with HPT had surgery. All had single parathyroid adenomas. Preoperatively these adenomas were localised on high-resolution ultrasound scan of neck but not on the sestamibi scan. The parathyroid adenomas were between 4-8mm in size. These patients also had nodular thyroid disease on ultrasound scan of neck but none had malignancy. In all seven patients serum Ca⁺ and PTH has stayed normal at 18 months follow up.

Despite the evidence that radiation exposure is linked to HPT, there are only few studies in the children who have been exposed to irradiation as a part of treatment for childhood malignancies. In this study there is a significant gender effect with females exhibiting higher levels of Ca⁺ than males. Serum Ca⁺ was significantly higher in patients who were survivors of haematological malignancies and those who had TBI as a single fraction for bone marrow transplant conditioning. Most centres now deliver TBI in multiple fractions. Many studies have reported that radiation-associated hyperparathyroidism (r-HPT) does not differ from HPT in general with respect to the age at diagnosis, sex distribution, mean serum calcium levels and characteristic symptoms [9,10]. After neck irradiation women have been reported to have twice the relative risk of men of developing HPT [11] but a marked sex difference in serum calcium levels as in this study has not been highlighted previously in r-HPT in survivors of childhood malignancies exposed to radiation. In 2001, a Tromsø population based study reported determinants of serum calcium in men and women in a health survey. 27,159 subjects were examined. The survey included measurements of serum calcium and questionnaires on diet and lifestyle factors. In males mean serum calcium declined from 2.41 mmol/l for those in their 20s to 2.34 mmol/l for those in their 80s. In females mean serum calcium was stable at a level of 2.35mmol/l before the menopause, and thereafter reached a plateau of 2.39mmol/l. The authors were unable to explain this change and biological significance in serum calcium level of more than 0.02mmol/l by any of the confounding factors [12].

Tumorigenic effects of radiation mostly result in malignant tumours but in parathyroid gland exposed to radiation there is higher frequency of benign tumours and low susceptibility to malignant transformation. Overall, parathyroid glands seem to have a relatively low sensitivity to radiation and induced changes may not become manifest until many years after irradiation. The

Table 3: Hematology and non Hematology Malignancies.

Variable	Hematology	Non-hematology
Number	74	31
Male	36	15
Female	38	16
Age at study (Years)	25.5±4.3	26.1±7.1
Age at diagnosis (Years)	9.03 ± 4.8	10.03 ± 9.5*
Radiotherapy	39	22
Mean dose of radiation (GY)	10.39 ± 11.3	31.8 ± 40.6*
Total body irradiation	23	0*
Free T4 (12-24 pmol/l)	14.6 ± 6.8	15.7 ± 4.7
TSH (0.4-4.0 mu/l)	2.3 ± 2.1	1.13 ± 1.2
Serum calcium (2.17-2.47mmol/l)	2.37±0.15	2.28 +0.10*
PTH (1.1 - 6.9 pmol/l)	4.84±2.77	4.48 +2.17

Free T4: Free thyroxine, TSH: Thyroid Stimulating Hormone, PTH: Parathyroid Hormone

delayed recurrent disease may suggest that not all parathyroids manifest the same degree of radiosensitivity, even in the same patient [9]. The distribution of histopathological types is reported to be very similar to general HPT [13]. The majority of patients with r-HPT are frequently asymptomatic and have higher incidence of thyroid disease particularly carcinoma [14,15].

The 40-year interval between radiation treatment and HPT in the initial case of HPT and radiation exposure reported by Rosen et al., [4] suggested a long latency period. Studies of patients with clinically evident HPT and radiation exposure have noted variable latency periods of 42 years [16], 39 to 45 years [17] and 35 years [9]. In a recently published study of a small group of radiation-exposed patients, the authors found a latency period of 46 years in the male patients and 49 years in the female patients. Most of the studies suggest a latency period for the development of HPT longer than that for thyroid disease [18]. Many of the studies on radiation exposure and endocrine disease focus on populations of patients who were exposed to radiation for the treatment of benign conditions in childhood. The average time since exposure to radiation and diagnosis of HPT in the current study was 16.2 ± 3.2 years. Published studies seem to support the hypothesis that HPT may develop more rapidly in patients who are treated with radiation as adults. In a study, which looked at the latency period separately for childhood and adult radiation exposure it was noted that, patients who were exposed as children, no case of HPT was diagnosed earlier than 25 years after the radiation treatment with an average lapse of 42 ± 11 years. In patients who were exposed as adults, the lapse between radiation and the diagnosis of HPT was 12 years. All of the patients in the quoted study underwent radiation therapy for benign disease [16]. A recently published study in children who had head and neck irradiation for childhood malignancy documented a significant risk of HPT and in shorter time frame. Authors concluded that the combination of high dose of radiation and young age put childhood survivors of malignancy at a high risk of parathyroid disease [19]. Overgrowth of parathyroid tissue may develop soon after treatment with high-dose radiotherapy. In a study that followed the serum PTH concentrations in patients who were treated with cancer therapeutic doses of radiation to the head and neck a trend was noted towards increasing PTH levels over the 3-year follow-up period. None of these patients had HPT during this relatively short follow-up period of 3 years after radiation therapy but the rising PTH concentrations suggested that these patients are at risk of developing of HPT in the future [20].

A positive correlation between the dose of radiation and the probability of experiencing HPT has been reported but no relationship has been noted between the radiation dose and the length of the interval period [11]. In the current study the total radiation dose was significantly higher in non-haematological malignancies where it was mostly given in multiple fractions than in haematological malignancies where it was frequently used as a single fraction TBI although the practice has now changed. The female patients in the haematological malignancy group had a higher serum Ca^{+} concentration. All the patients who developed HPT were females and had received TBI as a single fraction. Majority of these patients were asymptomatic.

HPT appears to be mild following radiotherapy. Many

patients go undetected for years until routine laboratory studies are checked or until the disease is suspected because of the development of kidney stones or osteoporosis. A significant correlation has been reported between the tumour weight and plasma Ca^{+} level [21].

So far seven patients have undergone parathyroidectomy. Parathyroid adenomas were evident on high-resolution ultrasound scan of neck but not localised on the sestamibi scan. Studies of sestamibi localization report sensitivities between 60% and 90%. Parathyroid gland size and weight has significant effect on the results of sestamibi scans. At a parathyroid gland size of less than 2 cm sestamibi scans become difficult to interpret [22]. Bone mineral density measurement in these patients was consistent with osteopenia. A high prevalence of low bone mineral density based on population normative data has been reported in this group of patients [23]. The causes for osteopenia in this group of patients are multifactorial. Four of these patients had right inferior parathyroid adenomas and three had right superior adenomas with typical histology. The parathyroid adenomas were small between 4-8mm in size. Location of a parathyroid adenoma in an upper gland has been reported to be significantly more common in patients with r-HPT as compared to the patients with p-HPT. This distribution of adenomas may correlate with the radiation treatment field. There was no evidence of thyroid malignancy in any of the patients but thyroid appeared nodular in six of these patients. In patients with r-HPT, preoperative diagnosis of associated thyroid disease by clinical and ultrasound evaluation is mandatory. Thyroid cancers with p-HPT occur nine times more frequently in irradiated patients than in non-irradiated patients [24]. Concomitant thyroid abnormalities can be present in 84% of patients with r-HPT and in 49% of patients with p-HPT [25]. According to the proceedings of the third international workshop on HPT, patients with asymptomatic HPT who are young and have evidence of low BMD should be referred for surgery. Parathyroid surgery is cost effective and associated with high rate of cure when performed by an experienced endocrine surgeon. Negative imaging should not preclude surgical referral or intervention [26].

Suspicion of r-HPT used to be an absolute indication for all four parathyroid gland exploration. It is now known that there is a high rate of single adenomas in r-HPT and that HPT is mild. Compared with "classic" biochemical p-HPT in such patients, operative failures may be higher [27]. In the absence of thyroid disease and positive localization on imaging, minimally invasive parathyroidectomy appears to be effective.

Based on our observation, increased awareness of the HPT in the survivors of childhood malignancies exposed to irradiation should lead to more aggressive screening for HPT in this group of patients.

CONCLUSION

In summary, this study suggests that there is a significant risk of HPT particularly in females with hematological malignancies who receive total body irradiation as a single fraction for bone marrow transplant conditioning. HPT in such cases is mild and the majority of these patients are asymptomatic. Parathyroid adenomas are usually single and small, thus localization on the

sestamibi scan may not be helpful. Patients exposed to irradiation in childhood should have lifelong surveillance of thyroid and parathyroid disease. Serum calcium, PTH, thyroid function test, neck ultrasound scans and measuring bone mineral density should be a part of follow up screen in this group of patients. All young patients with thyroid or parathyroid disease should be asked about a history of radiation exposure and patients with radiation-associated thyroid disease should be screened for HPT. The study also recommends the change of focus from radiation induced thyroid disease to radiation induced thyroid and parathyroid disease in late effects follow up. The retrospective nature of the study and the absence of vitamin D measurements in all patients who had radiation exposure do not allow conclusions regarding the prevalence of HPT in this group.

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