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ABSTRACT

Objective: During the first half of the 20th century, scalp irradiation was a standard treatment for children suffering from Tinea Capitis. These children are now more than 50 years old, reaching the age when manifestations of atherosclerosis are common. We investigated the possible association between childhood low dose scalp irradiation and development of carotid atherosclerosis in adulthood.
Methods: The study included 145 individuals treated by irradiation in their childhood, and 150 matched control subjects with no history of irradiation. The occurrence of stroke was disregarded during the inclusion. B-mode ultrasound imaging and US Doppler were used to measure carotid, femoral (distant from the radiated area) and intima media thickness (IMT). Blood lipids and homocysteine were also evaluated.
Results: No significant differences in the baseline patients' characteristics were observed. There were no differences in incidence of femoral IMT or prevalence of femoral stenosis between the groups. However, in the carotid of the irradiated group, a significantly elevated IMT and significantly increased prevalence of carotid stenosis were observed ($p < 0.001$). In the irradiated group, 30.3% and 39.3% had stenosis in the right or left carotid arteries, compared to 12.7% and 16% in controls($p < 0.001$), adjusted OR = 5.36[CI:2.78–10.33]. More participants in the irradiated group had experienced ischemic stroke: 13 patients (9%) from the irradiated group vs. 3 patients(2%) from the non-exposed group, $p = 0.01$.
Conclusions: Childhood scalp irradiation is a significant and thus far underestimated risk factor for adult carotid atherosclerosis disease. Physicians should be aware of the existence of such high risk populations.

1. Introduction

During the first half of the 20th century, scalp irradiation was a standard treatment for induction of epilation in children suffering from Tinea Capitis (an essentially benign fungal disease, also known as scalp ringworm) that is highly prevalent in crowded areas [1–3]. Between 1948 and 1960, this treatment was administered in Israel and abroad to thousands of prospective new immigrants [3]. Employment of irradiation for treating this disorder has been terminated in 1960, since oral method of therapy became available. Follow up studies within the adult population of irradiated in their childhood subjects demonstrated an increased risk of head and neck tumors and leukemia in the exposed population, compared to non-exposed to irradiation control subjects [4–10].

External high radiation therapy for head and neck cancer can lead to premature atherosclerosis that involves extensive areas of the common and internal carotid arteries [11,12]. Recently, a report from the Childhood Cancer Survivor Study indicated that survivors of childhood leukemia and brain tumors are at an increased risk of stroke [13]. The mean estimated dose related to progression of atherosclerotic disease or stroke in these studies was 50–60 Gy [11–13]. The relation between radiation and atherosclerosis was also investigated among 1804 survivors of the atomic bomb in Hiroshima [14]. The mean dose for exposed subjects was 794 mGy

Abbreviations: CCA, Common carotid artery; ICA, Internal carotid artery.

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for men and 701 mGy for women, and the age range at atherosclerosis examination was 55–95 years. Multivariate analysis showed that an elevated risk of about 30%, both for males and females, was associated with 1 Gy increment of radiation dose for aortic calcification. However, no association was found between exposure to radiation and carotid IMT. In our study population, the average dose administered to the carotid area was 9.3 cGy (range of estimated irradiation dose to the thyroid was 4.5–49.5 cGy), while irradiation of femoral arteries was negligible [6,15].

The aim of the present study was to investigate possible delayed effects of low dose scalp irradiation at childhood on carotid artery atherosclerotic disease in adulthood. Along with comparison of irradiation-exposed group to non-exposed subjects, the femoral arteries of radiation-exposed subjects, which were distant from the irradiation area, served as additional controls.

2. Methods

2.1. Study population

The study included 145 subjects with a proven record of been treated as children for Tinea Capitis by scalp irradiation in 1950's, and 145 pair-matched subjects who were never exposed to scalp irradiation in childhood. This sample size was determined under the following assumption: power of ≥95%, alpha error level-5, and 10% prevalence of carotid stenosis in the non-exposed group and minimal OR of 2.5.

Recruitment of the irradiated group was achieved with the help of community health care workers, notified about the study goals and target population. Another source for recruitment was a study population participating in an epidemiological survey conducted by National Institute for Tinea Capitis Research. This group included individuals who had been listed in the Modan files [7].

Non-exposed to irradiation control group was recruited from a database of about 700 individuals aged 50–75 years, summoned for a general cardiovascular evaluation to the Endothelial Dysfunction Clinic in Assaf Harofeh Medical Center. This clinic has been offering for 2 years now a free of charge cardiovascular risk evaluation to general population in Israel. The irradiated and non-irradiated participants were pair-matched by gender, age (±2 y), diabetes mellitus and ischemic heart disease (history of myocardial infarction or any revascularization procedure). The presence or absence of ischemic stroke was disregarded during the inclusion to the study. The study was approved by Local Ethics Committee for Human Trials, and all patients gave a written informed consent prior to their inclusion in the study.

2.2. Duplex ultrasound evaluation

Carotid and common femoral B-mode ultrasound recordings were obtained from each patient using the standardized protocol of the Atherosclerosis Risk in Communities (ARIC) study [16–18]. In brief, patients were positioned supine in a dark quiet room. Their right and left carotid and common femoral arteries were examined in supine midline position, tilted slightly upward. A 10 MHz linear-array probe was used with the GE Logic 7 Imaging System. The probe was manipulated so that both the closest and the most distant artery walls were in parallel positions and the lumen diameter was maximized horizontally. Landmarks were identified, and high-resolution, high-frame-rate images were recorded digitally in a cine-loop format for subsequent measurement without data degradation. Analyses were based on mean IMT of the far wall for 1 cm lengths of the common carotid bifurcation. Common carotid and femoral artery intima-media thickness (IMT) were measured in 12 predefined segments (6 per each side).

B-mode ultrasound imaging and Doppler US was used to measure carotid and femoral index and to calculate percentage of stenosis. Presence of stenosis was defined as percentage of stenosis ≥ 30%. The percentages of stenosis were evaluated by carotid duplex US evaluation. B-mode ultrasound imaging and Doppler US were use to measure carotid peak internal carotid artery velocity and calculation of the percentage of stenosis using the US image. All measurements were performed by a highly experienced vascular technician that was blinded to the patient's irradiation history. In order to maximize reproducibility of the results, all the recordings and all measurements were performed by the same technician.

2.3. Cardiovascular risk evaluation

After the US Doppler examination, all the participants had a complete physical examination, and their blood pressure, pulse, weight, height, current medications and medical history were recorded. Blood samples, 10 ml, were procured for assessment of creatinine, total cholesterol, high density lipoproteins (HDL), triglycerides (TG), calculated low density lipoproteins (LDL) and homocysteine.

2.4. Statistical analysis

Continuous variables were expressed as means ± standard deviations and statistical differences between the irradiated and non-exposed groups were evaluated by unpaired Welch's t test. Comparison of categorical parameters was performed by Chi square or by Fisher's exact test. Two dependent variables were evaluated: the presence of any percentage of stenosis exceeding 30% (dichotomous variable) and Intra Media Thickness (IMT) (tertiles and continuous). IMTs values were classified into tertiles: low, medium and high IMTs (separately for femoral and carotid). The effects of the main variable of interest i.e. radiation on the presence of any stenosis in the carotid and in the femoral arteries were assessed by logistic regression models.

Polytomous logistic regression models were used to evaluate the effect of radiation on the three categories of the carotid and femoral IMTs. IMT values were also examined as continuous variable by applying generalized linear models. Since the IMT values did not distribute normally in this sample, values were logarithmically transformed and estimates of the ratio and 95% confidence intervals were obtained by taking the antilog of the logarithmically transformed values.

For each dependent variable, three types of ORs were calculated to assess the effect of radiation: crude, adjusted for the matching variables (age, gender, ischemic heart disease and diabetes mellitus) and a full model including additional independent variables that were found to be at a significant level of ≤0.1 in the univariate analysis (smoking, family history of CVD and cerebrovascular disease).

3. Results

During the study period (July, 2004 January, 2006), a total of 186 subjects with proven and recorded history of irradiation in childhood were identified. The compliance rate was 78%, so that a total of 145 subjects were finally included in the irradiation group. Their mean age was 58.4 ± 5.4 years, 74 patients (51%) were males, 11 patients (7.6%) had a history ischemic heart disease, 40 patients (27.6%) had hypertension, 19 (13.1%) patients had diabetes mellitus and 35 (24.1%) patients had hyperlipidemia. The mean age at irradiation, based on the patients' anamnesis, was 7.17 ± 3.19 years.

Table 1
Description of demographic life style and selected medical characteristics by study group.

Variable	Irradiation ($n = 145$)		Control ($n = 150$)		P value
Gender [male (%)]	74	(51.0)	71	(47.3)	0.5
Age [years, mean ± SD]	58.0 ± 5.4		58.4 ± 6.5		0.6
Smoking [number (%)]	26	(17.9)	39	(26.0)	0.1
Ischemic heart disease [number (%)]	11	(7.6)	14	(9.3)	0.6
Diabetes mellitus [number (%)]	19	(13.1)	19	(12.7)	0.9
Hypertension [number (%)]	40	(27)	39	(26)	0.8
Hyperlipidemia [number (%)]	35	(24.1)	36	(24.0)	1.0
Cerebrovascular disease* [number (%)]	13	(9.0)	3	(2.0)	0.01
Positive family history for CVD# [number (%)]	7	(4.8)	28	(18.7)	<0.001
Biochemistry					
LDL cholesterol [mg/dL, mean ± SD]	114.4 ± 31.0		114.6 ± 30.2		1.0
HDL cholesterol [mg/dL, mean ± SD]	55.5 ± 14.4		56.7 ± 15.0		0.5
Triglycerides [mg/dL, mean ± SD]	135.6 ± 81.3		135.5 ± 88.5		1.0
Homocystein [mg/L, mean ± SD]	1.54 ± 0.47		1.45 ± 0.35		0.3

* Cerebrovascular disease = ischemic stroke as documented by brain computer tomography.
# CVD = cardiovascular disease.

Basal characteristics of the two groups are summarized in Table 1. No statistically significant differences in these baseline parameters were observed between the two study groups. One hundred thirty four patients (92.4%) of the irradiation group and 140 patients (93.3%) from the control group were Jewish immigrants from North Africa during 1950s. Incidentally, there was a higher percentage of family history of cardiovascular disease in the control group (4.8% vs. 18.7% in the irradiation and control groups respectively, $p < 0.001$).

Mean IMT and percentages of patients with ≥30% stenosis are summarized in Table 2. Mean femoral IMT was 0.80 ± 0.24 mm in the irradiation group and 0.80 ± 0.34 mm in the non-exposed group, $p = 0.9$. Within each group, no significant differences were found between percentages of right or left femoral stenosis. However, when the irradiated group was compared to control, a significantly elevated IMT and significantly increased prevalence of either right or left carotid stenosis were observed in the irradiated group. Mean carotid IMT was 0.68 ± 0.16 mm in the irradiation group and 0.61 ± 0.17 mm in the control group, $p < 0.001$. In the irradiated group, the percentages of patients with >30% stenosis in the right or left carotid arteries, were 30.3% and 39.3% vs. 12.7% and 16% in the control groups, respectively, $p < 0.001$ for both comparisons. In the femoral arteries there was no significant difference in the number of patients with more than 30% stenosis (Table 2). With respect to the patients with more than 50% stenosis, 20% in the irradiation group ($n = 29$) and 7.3% in the control group ($n = 11$) had more than 50% stenosis in at least one of the carotid artery ($p = 0.003$). For the femoral artery, no differences were found between the irradiated and the control groups (5.5%, $n = 8$ vs. 5.3%, $n = 8$; respectively, $p = 0.9$). In our study population there was no significant correlation between gender, radiation age (mean age at radiation was 7.17 ± 3.19 years), smoking or any head and neck cancer to the severity of the carotid atherosclerosis disease. Morphology of the carotid plaques in the irradiated group substantially differed from that in normal controls: the plaques found in the irradiated patients appeared more prolonged, irregular and ulcerated compared to the plaques observed in the control group. These differences, although not quantified, could be distinctly visualized. Fig. 1 demonstrates a typical atherosclerotic plaque within the carotid of a patient with a history of childhood scalp irradiation, with no cardiovascular risk (except for age) and no atherosclerotic plaques in the femoral arteries.

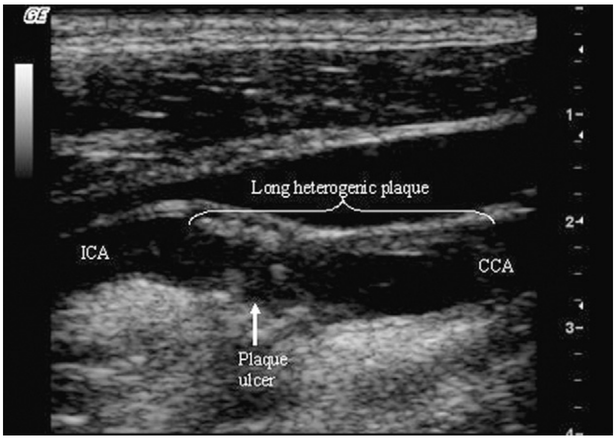

Fig. 1. Duplex ultrasound imaging of an irregular atherosclerotic plaque with pronounce ulceration within the carotid of a patient with a history of childhood scalp irradiation.

Table 2
Indices of duplex ultrasound of carotid and femoral arteries by study group.

Variable	Irradiation ($n = 145$)		Control ($n = 150$)		P value
Carotid[b]					
IMT [mm, mean ± SD]	0.68 ± 0.16		0.61 ± 0.17		<0.001
Right stenosis [number (%)]	44	(30.3)	19	(12.7)	<0.001
Left stenosis [number (%)]	57	(39.3)	24	(16.0)	<0.001
Femoral[a]					
IMT [mm, mean ± SD]	0.80 ± 0.24		0.80 ± 0.34		0.9
Right stenosis [number (%)]	11	(7.6)	14	(10.0)	0.5
Left stenosis [number (%)]	11	(7.6)	18	(12.0)	0.2

IMT-Intima media thickness.
[a] Femoral: both IMT and stenosis are measured in the common femoral arteries.
[b] Carotid: IMT – is measured in common carotid, stenosis is measured in the internal carotid.

Table 3
Odds ratio and 95% confidence intervals for radiation on the indices of duplex ultrasound of carotid and femoral arteries.

	Crude		Adjusted for matching variables*		Adjusted for matching variables and confounders**	
	OR	95% CI	OR	95% CI	OR	95% CI
Presence of any stenosis						
Carotid#	3.95	2.30–6.78	5.60	2.98–10.52	5.36	2.78–10.33
Femoral[a]	0.72	0.34–1.53	0.86	0.38–1.93	0.87	0.35–2.15
IMT (mm)						
Carotid#						
Low (≤0.567)	1.0		1.0		1.0	
Medium (0.568–0.650)	1.46	0.83–2.59	1.54	0.86–2.77	1.45	0.79–2.67
High (>0.650)	3.89	2.15–7.05	5.08	2.60–9.90	4.32	2.14–8.71
P for trend		<0.001		<0.001		<0.001
Femoral[a]						
Low (≤0.6609)	1.0		1.0		1.0	
Medium (0.661–0.790)	1.33	0.76–2.32	1.27	0.71–2.28	1.31	0.71–2.41
High (>0.790)	1.41	0.81–2.47	1.53	0.83–2.83	1.63	0.85–3.14
P for trend		0.23		0.17		0.14

IMT-intima media thickness.
[a] Femoral: both IMT and stenosis are measured in the common femoral arteries.
[#] Carotid: IMT – is measured in common carotid, stenosis is measured in the internal carotid.
[*] Matching variables: age, gender, ischemic heart disease and diabetes mellitus.
[**] Confounders: smoking, family history of cardiovascular disease and cerebrovascular disease.

Table 3 shows the effect of irradiation on frequency of stenosis and/or IMT of the carotid and femoral arteries in 3 separate models. Irradiation had significantly increased risk for carotid stenosis; adjusted OR = 5.36 [CI: 2.78–10.33], and had no significant effect on stenosis in the femoral arteries, adjusted OR = 0.87 [CI: 0.35–2.15]. Exposure to radiation significantly elevated the risk for carotid thickness (adjusted OR = 4.32 95% CI: 2.14–8.71 for highest IMT category compared to the lowest IMT, *p* for trend <0.001). No significant association between irradiation and IMT was demonstrated for the femoral arteries. When IMT was considered as a continuous variable, irradiation was associated with a 10% increase in the carotid IMT values (95% CI = 1.07–1.14) (data not shown). In accordance with the finding on the atherosclerotic disease in the carotid arteries, more participants in the irradiated group had experienced cerebrovascular disease (ischemic stroke), as documented by brain computer tomography: 13 patients (9%) from the irradiated group vs. 3 patients (2%) from the non exposed group, *p* = 0.01 (Table 1).

4. Discussion

The present investigation demonstrates that scalp irradiation performed in childhood, even at a low dose, represents a risk factor for the development of carotid stenosis due to atherosclerotic plaques in adult age. This conclusion is based on the data collected from a group of 50–70 year-old subjects, 145 of them exposed to scalp irradiation in their childhood and 145 serving as non-exposed controls. In 1940s and 1950s, scalp irradiation was a widely applied therapy for induction of epilation in children suffering from Tinea Capitis [1,2]. These children are now more than 50 years old, reaching the age when manifestations of atherosclerosis are notoriously common, and the risk factor of previous exposure to ionizing radiation should be taken in consideration in their general cardiovascular risk assessment. Major risk factors for carotid artery atherosclerosis, such as diabetes mellitus, smoking, hypercholesterolemia and positive family history of cardiovascular disease, are similar to the risk factors in any other vascular atherosclerosis [19,20] With respect to any of them, the two experimental groups did not differ statistically, with the exception of positive family history of cardiovascular disease prevailing in the control group, which will be discussed later.

Irradiation procedure applied to our study group subjects in their childhood was confined to the scalp area. We, however, evaluated IMT and/or stenosis signs not only in carotid arteries, which lied within the irradiated field, but also in the femoral arteries, far more distant from the irradiation-exposed areas. The latter was important since, as already mentioned, a selection bias of patients' choice could not be ruled out in this study. More so, this enabled us to distinguish between the local effect of ionizing radiation and that of the systemic potential risk factors. Close to the irradiated area, in carotid arteries, a significantly higher incidence of IMT and/or stenosis was observed in the irradiated patients' group. By contrast, atherosclerosis parameters examined in the femoral arteries to serve as controls for possible confounders, revealed no appreciable differences between the groups. Hence, systemic effects on atherosclerosis progression, as reflected by femoral IMT, were similar in both groups, and childhood scalp irradiation was the only significant independent risk factor for adulthood carotid atherosclerotic disease.

Ionizing radiation is a well known risk factor for the development of a variety of tumors [4–6,21–23]. A number of factors predictive of malignancies are known to be also associated with atherosclerosis [24]. The somatic mutation hypothesis of Benditt states that atherosclerotic plaques are monoclonal by origin. They start as benign neoplasms of the arterial walls and are most probably derived from a mutation of a single smooth muscle cell that acquired a proliferative advantage over sister cells [24]. A large proportion of pathologic changes in the intima, media, and adventitia after irradiation may be difficult to distinguish from typical atherosclerotic disease. It has been previously demonstrated that media is more severely damaged, while adventitia demonstrates greater thickening and fibrotic signs, in radiation-induced coronary disease compared to non radiation-induced coronary atherosclerosis [25]. Human necropsy observations also suggest the existence of some distinct mechanisms of intimal fibrous thickening and adventitial scarring in irradiated coronary arteries. [26]. In the present study, employing ultrasound Doppler imaging technique, carotid atherosclerotic plaques morphology in the irradiated patient group appeared to be more irregular and ulcerated than similar plaques in the control group. These differences, although not quantified, could be distinctly visualized (Fig. 1).

A number of cross-sectional and retrospective studies have shown that patients with a history of direct radiotherapy to the neck are at increased risk for developing significant carotid artery stenosis, with high proportion of related symptoms [11–13,27]. The annual progression rate, from <50% to >50% stenosis in irradiated arteries was reported to be 15.4%, compared with 4.8% in non-irradiated arteries (24%). Survivors of childhood leukemia and brain tumors were shown to be at an increased risk of stroke [13]. High doses of irradiation, 50–60 Gy, were used in these investigations [11–13,28].

For children treated with ionizing cranial irradiation for Tinea Capitis in Israel, the dosages were re-evaluated during the 1960s. Average doses to different organs were also individually estimated for each irradiated subject [15]. These assessments took into account age and gender, both highly correlated with the size of the child, center of application of irradiation beam, number of treatment sessions and, probably, of head movements during treatment [6,15]. The mean average dose applied to the area of the carotid artery (to the neck at level of the thyroid gland) for all irradiated individuals was 9.3 cGy (range 4.5–49.5 cGy), indicating that our study population was exposed to relatively lower dose of radiation. However, our population was subjected to a longer follow up period compared to most of the previously published studies, so the delayed damage became unequivocally evident. In this respect, it is noteworthy that now day's carotid arteries may be quite frequently exposed to low dose irradiation during various imaging procedures. For example, during standard neck CT the radiation dose to the carotid area is around 2.65 cGy [28] and during angiography of the carotid arteries the dose can reach 8.8 cGy [29]. It may be possible that in the long run these relatively low doses may also have a significant pathophysiologic effect on the carotid arteries. This observation definitely calls for further investigations.

The present study has several limitations. Mainly, the population groups (both exposed and non-exposed to irradiation) might have not been sufficiently representative for the target populations. The radiation exposed group has been recruited mostly by public health care workers, and thus cannot really be considered a sample randomly chosen from the total adult population subjected to scalp irradiation in early childhood. However, the relatively high compliance rate of this group (78%) may indicate that no selection bias existed regarding our main variable of interest, namely the presence of atherosclerosis disease. In turn, the control group was chosen from the database of the Endothelial Dysfunction Clinic at Assaf-Harofeh Medical Center. The Clinic's goal was to collect and scrutinize the data related to cardiovascular risk factors within the general Israeli population, so some unintentional bias in choosing this population also might have happen. However, the two study groups did not differ with respect to any secondary risk factors associated with atherosclerosis. In addition, as mentioned above, the irradiated group proved to be at high risk only for atherosclerotic disease of carotid (close to the irradiation area), not of the femoral artery (representing the systemic effects).

Taken collectively, the main conclusion would be that childhood scalp irradiation is an independent risk factor for carotid atherosclerosis disease in adulthood. We believe that this risk factor has been thus far underestimated, and that practicing physicians should be aware of the existence of such high risk populations. It seems rational that in these patients aggressive therapy against other atherosclerosis risk factors, such as cholesterol and blood pressure, in combination with anti-platelet therapy, as well as the possibility of vascular intervention, would be beneficial. Further studies are in order to establish the optimal policy for appropriate screening, surveillance and care for this patient category.

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