Radioiodine therapy increases the risk of cerebrovascular events in hyperthyroid and euthyroid patients

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Abstract

Background and objective: Hyperthyroid patients treated with radioiodine have increased morbidity and mortality from cerebrovascular events. This risk has until now has been attributed to the hyperthyroidism. However, radioiodine therapy of benign thyroid diseases exposes the carotid arteries to radiation and is capable of inducing atherosclerosis. The objective of the study was to elucidate whether ionizing radiation from radioiodine might contribute to cerebrovascular morbidity.

Methods: In a retrospective register cohort study, 4000 hyperthyroid and 1022 euthyroid goitre patients treated with radioiodine between 1975 and 2008 were matched 1:4 on age and sex with random controls. The cohort was followed from the date of treatment until hospitalization due to cerebrovascular event, death, 20 years of follow-up or March 2013. Data were analyzed in competing risk models adjusting for age, sex, Charlson's comorbidity score, atrial fibrillation and previous cerebrovascular events.

Results: Mean follow-up time was 11.5 years, mean age 61 years, with a total number of 3228 events. Comparing all radioiodine-treated patients with controls, the fully adjusted model showed increased risk of cerebrovascular events among all treated patients, hazard ratio (HR) 1.18 (95% CI 1.09–1.29). The risk was increased among hyperthyroid (HR 1.17; 95% CI 1.07–1.28) as well as euthyroid patients (HR 1.21; 95% CI 1.02–1.44).

Conclusions: We report an increased risk of cerebrovascular events in hyperthyroid as well as euthyroid patients treated with radioiodine for benign thyroid disorders. That these patient groups have similar risks suggests the possibility that radiation from radioiodine contributes to cerebrovascular morbidity via acceleration or initiation of atherosclerosis.

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Introduction

It is recognized that ionizing radiation induces or accelerates the development of atherosclerosis when arteries are exposed. An increased risk of atherosclerotic events can be seen already from the first years after exposure (1). As the thyroid and carotid arteries are in close contact, the carotid arteries are very likely to be exposed to radiation during treatment with radioactive iodine (RAI) for benign thyroid disorders (2). This raises

the concern that these patients might have an increased risk of atherosclerotic cerebrovascular events, i.e. stroke.

Indeed, an increased risk of mortality from cerebrovascular events has been shown in studies of hyperthyroid patients treated with RAI (3, 4) (hyperthyroid defined as a thyroid-stimulating hormone (TSH) <0.01 and elevated free thyroid hormones (tri-iodothyronine (T₃) and/or thyroxine (T₄)). This risk has been attributed to the

hyperthyroidism not RAI, as hyperthyroidism has many established vascular effects such as hypercoagulopathy (5), increased risk of atrial fibrillation (AF), increased left ventricular ejection fraction and heart failure (6). The theory that it is the hyperthyroidism *per se* that holds the risk is supported by Sheu *et al.* (7), who demonstrated an increased risk of stroke among hyperthyroid treated with anti-thyroid medicine. However, other studies of hyperthyroid patients treated with RAI, surgery and/or medical treatment have described a relationship between hyperthyroidism and cardiac – but not cerebrovascular mortality or morbidity (8, 9, 10, 11, 12). Unfortunately, data on cerebrovascular events in euthyroid goitre patients treated with RAI for symptoms such as compression of trachea or dysphagia are absent. Data on this type of patients could, perhaps, have given us an indication on whether it is hyperthyroidism *per se* or RAI that leads to the increased risk of cerebrovascular events in RAI-treated hyperthyroid patients.

As a cerebrovascular event is serious, we find this possible adverse effect of RAI important to examine. Should an excess risk exist, it would be an important factor to take into account when making the decision to treat with either thyroidectomy or RAI. Another important aspect is that the patients should be properly informed on effects and possible serious side effects before accepting any of the treatments.

Objectives

Therefore we wanted to elucidate to what extent RAI might be a factor in the increased risk of cerebrovascular events among RAI-treated hyperthyroid patients. Thus, we aimed to investigate whether there was a difference in the hazard ratio (HR) of hospitalization from cerebrovascular events between RAI-treated patients, both hyperthyroid and euthyroid, compared with random thyroid healthy controls.

Subjects and methods

Study population

A database of 5203 patients treated with RAI for benign thyroid disease was established. The patients were at least 18 years of age, treated with RAI between 1975 and 2008 for either hyperthyroidism or symptomatic goitre at three university hospitals in Copenhagen, Denmark. Date of birth, date of first RAI treatment, administrated dose of ^{131}I , thyroid status (hyperthyroid or euthyroid) and

scintigraphic and/or ultrasound characteristics (i.e. diffuse or multi nodular) were registered throughout the years. The patients were categorized as euthyroid if they had a TSH >0.1 , never been hyperthyroid and not on any thyroid medication, and were classified as hyperthyroid if they had a biochemically confirmed diagnosis of overt hyperthyroidism or if they had a TSH below 0.1 mU/l measured at least twice while not on any thyroid medication.

The patients, with unknown thyroid status ($n=44$), receiving a total administrated dose of ^{131}I over 2000 MBq ($n=60$), who had an invalid identification number ($n=68$), and patients with ambiguous data ($n=2$) were excluded (see Fig. 1). The characteristics of the excluded subjects were no different than the rest of the patients. The aimed target dose to the thyroid was between 90 and 150 Gy, depending on the characteristics of the thyroid. Exclusion of patients receiving more than 2000 MBq was done to mimic a normal treatment of benign thyroid disease in Denmark. In this study, the standard treatment regime is one dose of 200–600 MBq (with a maximum of 600 MBq according to outpatient radiation protection regimes). Some patients will however need a second dose (and a few even more) due to treatment failure.

Resident citizens in Denmark have a unique identification number in the Danish Civil Registration System linking hospital contacts through the Danish National Patient Registry (13). All remaining cases with a valid identification number were included ($n=5135$). The patients were matched 1:4 on age and sex with four randomly selected controls from the Danish background population through the Danish Civil Registration System ($n=20\,540$). All controls had to be without known thyroid diagnosis in the Danish National Patient Registry and alive on their

Figure 1
Flowchart of inclusion.

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index patient's day of treatment. Four controls per case were chosen to optimize the sample size and the statistical power of the study.

The study and the database were both approved by the local data safety section (GLO-2012-25) and by the national data safety section (FSEID-00000388).

Outcome

The primary outcome was defined as a difference in HR of the combined endpoint of hospitalization from cerebrovascular events among controls, hyperthyroid and euthyroid. Cerebrovascular events were defined as stroke (not haemorrhagic stroke in ICD10), transient ischaemic attack (TIA) and amaurosis fugax. Secondary outcomes were defined as the difference between all RAI-treated patients and controls, and between hyperthyroid and euthyroid when compared directly. We did not perform a dose-response analysis between administered dose of ¹³¹I and main outcome as there is no simple relationship between administered dose and absorbed dose to the carotid arteries (2).

All cases and controls were followed from day of RAI until cerebrovascular event, death, emigration, maximum of 20 years follow-up or end of follow-up period on the 10th March 2013, whichever occurred first.

Information on the outcomes (and comorbidity) was obtained through National Patient Registry by use of identification numbers and prespecified ICD codes (see Table 1). In the National Patient Registry, an individual's hospital discharges are diagnosed with a primary diagnosis

is of ICD8 (up until 1994) or ICD10. The diagnoses of cerebrovascular diseases have been validated in the National Patient Registry and have a relatively moderate-to-high positive predictive value of about 80% for stroke and 65% for TIA (14). Data on date of death were obtained through death certificates in Danish National Death Register and Danish Civil Registration.

Comorbidity

Comorbidity, such as diabetes, rheumatic disease and heart disease, were identified through the National Patient Registry (see Table 1). Components of the Charlson comorbidity score (CCS) until inclusion date was retrieved, and an individual comorbidity score was created. The CCS has been validated to some extent for prediction of outcome after stroke (15). The ICD coding of CCS in the National Patient Registry has been validated (16).

Information on lipid profile, family history and social economical status was not available for neither patients nor controls. Furthermore, we do not have data on smoking status on neither the hyperthyroid nor the control group. However, we have smoking data for ~20% ($n=193$) of the euthyroid patients included in this study from another ongoing study (J L la Cour, U B Andersen, C H Sorensen, B Nygaard and L T Jensen; unpublished observations, registration number at the Ethical Committee in the Capital Region of Denmark: H-1-2012-120). In this euthyroid subgroup, the number of active smokers is comparable with the Danish

Table 1 ICD codes used in study.

Disorder	ICD8	ICD10
Main outcome		
Stroke	432–434; 436–438	I63–68
Transient ischaemic attack	435	G54–59
Amaurosis fugax	377.02	H34; G453
CCS		
Cerebral vascular disease	430–438	I60–69; G45–46
Peripheral vascular disease	440–445	I70–74; I771; R02
Myocardial infarction	410	I21–23; I25
Congestive heart failure	427.09; 428.99; 782.49	I42–43; I50; I51.7; I110; I13.0
Malignancy	140–209	C00–97
Diabetes	249–250	E10–14
Pulmonary disease	490–492; 515.99–518	J41–68; J82–83; J84.1; J98.2; J98.3
Dementia	290; 293.09	F00–03; F05.1; G31
Mild liver disease	456–457; 570–571; 573.1; 573.4	B15.0; B16; K70–74; K76; I85
Hemiplegia	344	G81–82
Renal disease	403–404; 582–584; 590; 593.19; 753; 792	I12–13; N0–5; N7; N11; N14; N17–19; Q64
Rheumatic disease	135.99; 446; 712; 714.95–716	M05–06; M08–09; M30–36; D86
Ulcer	530.91; 530.98; 531–535	K22; K25–29
AIDS	079.83	B21–24

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background population (19% vs 21%; Statistics Denmark, <http://www.dst.dk/da/Statistik/emner/de-kommunale-serviceindikatorer/sundhed>, accessed 24th October 2014).

Statistical analyses

All baseline data are presented as percentages for categorical data and for continuous as means $\pm$ s.d. when data followed a normal distribution or medians and interquartile range (IQR) when they did not.

Overall risk of being hospitalized with a cerebrovascular event was illustrated using Kaplan–Meier failure plot and log-rank testing for the comparison between groups. Competing risk regression with death as the competing risk was used to test the risk of hospitalization due to cerebrovascular events among hyperthyroid, euthyroid and controls adjusting for risk factors of age and sex in a basic model. In the final model, CCS (≥ 2), AF and previous cerebrovascular event as categorical variables (yes/no) were included. Model control was done by plotting proportional hazards.

All statistical analyses were performed with SAS Statistical Software version 9.3 (SAS Institute, Cary, NC, USA) or Stata Software version 11 (StataCorp., College Station, TX, USA). A two-sided *P* value <0.05 was considered to be statistically significant.

Sensitivity analyses ► A separate test was done for stroke alone (not including amaurosis fugax and TIA) in the full competing risks model, to ensure that the most important endpoint was consistent with the test of the combined endpoint. To see whether there was more systemic

atherosclerosis in the RAI-treated groups than in the control group, we tested the risk of developing acute myocardial infarction (ICD8: 410 and ICD10: I21–22) after inclusion by a log-rank test and by Mantel–Haenszel analysis adjusted for age, sex, prior ischaemic heart disease, AF and CCS (data did not fit the assumptions of competing risk).

Furthermore, we tested whether treatment year influenced the HR by splitting on treatment year as different treatment regimens may have been applied. In addition, we tested whether diffuse or multi-nodular thyroid disease influenced the risk of cerebrovascular events.

Results

A total of 25 562 subjects, 14.3% men, were followed with a mean follow-up time of 11.5 years (± 6.1) and a total number of person years at risk of 294 230. The mean age at inclusion was 61 years (± 14.2), and the total number of events were 3228. Before or on the day of inclusion, 468 (1.8%) subjects had been diagnosed with AF, and 1305 (18.6%) had a CCS of two or more. Both the RAI-treated groups had more comorbidity than the control group, and the euthyroid group was younger than the other groups (see Table 2).

When testing whether there was a difference between the control group and the whole RAI-treated group (including both the hyperthyroid and the euthyroid), we found a significant difference using Kaplan–Meier failure plot and log-rank testing ($P < 0.001$). In the basic competing risk analysis model (adjusting for age and sex), the RAI-treated group had an increased risk of

Table 2 Characteristics of the included patients and controls. Number of events denotes the absolute number of hospitalizations from cerebrovascular disease (stroke, transient ischaemic attack and amaurosis fugax) for each group. Charlson comorbidity score (CCS) is an individual score of comorbidity using 19 different diseases giving them a point from 1 to 6 and from that generate one score from 0 to 6 per individual. Atrial fibrillation (AF) refers to persons with the disease registered before or at time of treatment. Total dose of ¹³¹I refers to the individual patients accumulated dose of ¹³¹I given at the three included hospitals from 1976 to 2008.

	Control (n = 20 540)	Hyperthyroid (n = 4000)	Euthyroid (n = 1022)	Total (n = 25 562)
Person time at risk (years)	238 367	43 790	12 073	294 230 [†]
Subjects with a cerebrovascular event after inclusion, n (%)	2508 (12.2%)	584 (14.6%)	136 (13.3%)	3228 (12.6%) [†]
Age at inclusion, mean years (s.d.)	61.0 (14.2)	61.9 (14.3)	57.8 (13.3)	61.0 (14.2)*
Sex (male), %	14.3	14.7	12.1	14.3
CCS ≥ 2 (%)	4.7	7.0	6.3	5.1 [†]
AF (%)	1.5	4.9	3.4	1.8 [†]
Total dose of ¹³¹ I, median MBq (IQR)	–	400 (304)	407 (303)	400 (304)*
Subjects with a cerebrovascular event before inclusion date (%)	3.8	4.8	4.0	4.0*

* $P < 0.05$ and [†] $P < 0.001$ for difference between the groups.

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Table 3 The results from the main competing risk analyses of risk of hospitalization from cerebrovascular events (combined endpoint of stroke, transient ischemic attack and amaurosis fugax) after therapy with radioactive iodine for benign thyroid disorders. Maximum follow up of 20 years. Death was the competing risk in all analyses.

Main results	Hazard ratio	
	In a model adjusted for age and sex (95% CI)	In a model adjusted for age, sex, CCS, AF and previous cerebrovascular event (95% CI)
All RAI treated vs control	1.21 (1.11–1.31)	1.18 (1.09–1.29)**
Patient groups compared with controls		
Hyperthyroid	1.20 (1.1–1.32)	1.18 (1.07–1.29)**
Euthyroid	1.23 (1.04–1.46)	1.22 (1.02–1.44)*
Hyperthyroid vs euthyroid	0.97 (0.8–1.17)	0.96 (0.8–1.16)

* $P < 0.01$; ** $P < 0.001$.

cerebrovascular events compared with controls of hazard ratio (HR) 1.21 (95% CI 1.11–1.31; see Table 3). Adding CCS, AF and previous cerebrovascular event to the model only affected the estimates slightly, HR 1.18 (95% CI 1.09–1.29; see Table 3).

When testing whether the risk of cerebrovascular events was explained by thyroid status, we split the patient group into hyperthyroid and euthyroid and found a difference between the thyroid healthy control group and both the RAI-treated groups (hyperthyroid and euthyroid; log-rank testing, $P < 0.0001$). In the basic competing risk model, the hyperthyroid as well as the euthyroid had an increased risk of cerebrovascular events compared with the control group, with an HR 1.20 (95% CI 1.11–1.32) and HR 1.23 (95% CI 1.04–1.46) respectively (see Table 3). It only changed the estimates slightly when we adjusted for CCS, AF and previous cerebrovascular event, HR 1.17 (95% CI 1.07–1.29) for hyperthyroid group and HR 1.21 (95% CI 1.02–1.44) for euthyroid group (see Table 3 and Fig. 2). When testing hyperthyroid and euthyroid against each other, we find no difference (see Table 3).

Sensitivity analyses

The separate analysis of stroke alone as outcome did not differ from the main analysis (data not shown). In terms of acute myocardial infarction, a difference was seen between the control and the hyperthyroid groups ($P < 0.0001$ for log-rank; relative risk (RR)=1.12 (95% CI 1.01–1.25); $P=0.034$ for Mantel-Haenszel), not between the control group and euthyroid group ($P=0.29$ for log-rank; RR=1.14 (95% CI 0.93–1.4); $P=0.2$). No difference was observed in the analysis on treatment year (data not shown) or when comparing diffuse and multi-nodular thyroid disease (data not shown).

Discussion

In this cohort study, we report an increased risk of cerebrovascular events after RAI in 4000 hyperthyroid and 1022 euthyroid patients compared with 20 540 controls followed for a total of 294 230 follow-up years. This is the first study evaluating the possible risk of RAI-induced cerebrovascular events differentiating between euthyroid patients and hyperthyroid patients.

Figure 2

Cumulative incidence of cerebrovascular events. Cumulative incidence of hospitalization from the combined endpoint cerebrovascular event (stroke, transient ischaemic attack and amaurosis fugax) after therapy with radioactive iodine (RAI) in a competing risk model adjusted for age, sex, atrial fibrillation, Charlson comorbidity score (CCS) and previous cerebrovascular event. Death is the competing risk. Patients (both hyper- and euthyroid) and controls enter at the day of the patients' therapy with RAI. Figure illustrates the difference among the hyperthyroid and euthyroid groups compared with the control group.

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The main finding is that euthyroid patients treated with RAI have increased risk of cerebrovascular events (stroke, amaurosis fugax and TIA) with a HR 1.22 (1.02–1.44) compared with the control group in our fully adjusted model. The risk is comparable with the established risk of cerebrovascular events and mortality among RAI-treated hyperthyroid (HR 1.18; 95% CI 1.07–1.29). If hyperthyroidism was the only explaining factor of the excess risk of cerebrovascular events, we would have expected to find a difference between euthyroid and hyperthyroid patients. None of the sensitivity analyses changed the confidence in our results. In fact, that the mechanism behind the increased risk of cerebrovascular events might be a local radiation effect, not a systemic reaction to RAI or difference in the general atherosclerosis burden between the groups, is strengthened by the information that the euthyroid group and the control group have similar risks of developing acute myocardial infarction. Our results therefore indicate that other factors than hyperthyroidism might explain the increased risk of cerebrovascular events in the RAI-treated group. As discussed, one of these factors could be radiation-induced atherosclerosis in the carotid arteries.

In order for RAI to induce atherosclerosis and thereby increase the risk of stroke, the carotid arteries have to be exposed during treatment. Through computer simulation, we have recently investigated whether this is in fact the case (2). We found that the carotid arteries are exposed to an average committed dose of 4–50 Gy/GBq ¹³¹I orally administrated with a dose rate of 4.2 Gy/GBq in a standardized situation (2). This amount of energy is well above the estimated lower limit of 2 Gy to induce an inflammatory response and initiate or accelerate atherosclerosis (17). This means that radiation-induced atherosclerosis could be an explanatory factor. That radiation-induced atherosclerosis could perhaps evolve after RAI is shown a study by Surucu *et al.* (18) who measure carotid intima media thickness (CIMT; a fairly validated surrogate for early atherosclerosis (19)) in hyperthyroid patients treated with RAI. They report a lasting increase in CIMT after RAI. However, the study has several limitations. First and foremost is that they do not account for changes in cholesterol and TSH, which are known to affect CIMT (20). However, the result does fall in line with our studies and studies comparable with our current epidemiological study.

In UK, Franklyn *et al.* (3) followed 7209 hyperthyroid patients treated with RAI and find a standardized mortality ratio of 1:4 (95% CI 1.2–1.5) for mortality from cerebrovascular events. Metso *et al.* (4, 21) followed RAI-treated

hyperthyroid and controls in Finland and find an increased risk of mortality and morbidity from hospitalization due to ischaemic and embolic cerebrovascular events (RR=1.31 (1.14–1.56) in (4), and 1.40 (1.16–1.69) in (21)). The finding of similar risk sizes across three RAI-treated hyperthyroid populations indicates a correlation. Still the results do not explain whether it is hyperthyroidism, RAI therapy or the combination that increases the risk.

Trying to help answer the question of hyperthyroidism vs treatment, Sheu *et al.* (7) found an increased risk of stroke of 1.44 (1.02–2.12) among young Taiwanese patients on thyroid medication. However, in Finland Ryodi *et al.* (8) did a register study on surgically treated hyperthyroid patients and found an increased risk of hospitalization from all-cause cardiovascular events, but not from cerebrovascular events ($P=0.057$). This strengthens our fear of RAI playing a role in the increased risk of cerebrovascular events after RAI. However, the results of these studies illustrate that the debate on treatment vs disease remains controversial.

Strengths and limitations

We did not have access to the actual TSH values. A cut off of TSH of 0.1 was used during categorization throughout the years. This leads to some of the mild subclinical hyperthyroid (defined as TSH below normal range but above 0.1 and normal T₄ and free T₃) being included in the euthyroid group. This could lead to an overestimation of the risk of cerebrovascular events in this group, as these individuals have an increased risk of AF (22). However, whether subclinical hyperthyroidism leads to an increased risk of stroke is a subject of debate. A cross-sectional study found an increased risk of stroke (23); however, a recent meta-analysis by Chaker *et al.* (24) and a recent very large study not included in the meta analysis by Selmer *et al.* (10) found no evidence of increased risk in subjects with mild subclinical hyperthyroidism. Therefore, whether this classification of TSH <0.1 leads to an overestimation of the risk of cerebrovascular events in our study due to mild subclinical hyperthyroidism is uncertain.

No post-RAI TSH levels were available, which is a limitation because there is a connection between thyroid function after RAI and survival (25). The study by Boelaert *et al.* finds that patients who develop a need for thyroid hormone substitution after RAI survive the longest. However, the connection between post-RAI TSH levels and cerebrovascular events is unknown, and it is therefore difficult to estimate how knowing these values would affect our results.

There may be a difference in comorbidity not requiring hospitalization between the groups, which we do not find, because we only include hospitalizations. Furthermore, some minor TIAs might be only treated at the general practice and therefore not included in our data. This would lead to an underestimation of the risk of cerebrovascular events in total. However, there is no reason to believe that more people in the control group would have one of these minor TIAs than patients in the two other groups. If anything, following our theory of radiation-induced atherosclerosis it would be the other way around. This would lead to an underestimation of the risk. However, given that we have more than 3000 events, the effects of these unrecorded TIAs are not likely to affect our results.

The problem of residual confounding is always there in the register-based design. We cannot account for differences in the socioeconomic status, traditional cardiovascular risk factors (i.e. cholesterol and obesity), and smoking status between the patients and the controls. As smoking and socioeconomic status are factors predisposing thyroid illness and stroke, these are expected to play a role in our findings, especially among the hyperthyroid patients (26). However, in our subpopulation of euthyroid patients the frequency of smokers was comparable with the background population. To our knowledge, there are no studies indicating increased prevalence of smokers among euthyroid treated with RAI compared with the general population. Therefore, the increased risk of cerebrovascular events in this group is not likely solely to be attributed to residual confounding.

A control group treated with a different modality, i.e. medication or surgery, would have made an even more convincing argument. These patients are unfortunately not included in our database, and even if they were, there would still be the problem with selection bias in a retrospective design.

The major strength of our current study is that we have a large cohort of both hyperthyroid and euthyroid patients treated with RAI followed in a highly validated register (14).

Conclusion

It is known that ionizing radiation can induce atherosclerotic events. During therapy, RAI exposes the carotid arteries to radiation. Therefore, RAI therapy might increase the risk of cerebrovascular atherosclerotic events. In this study, we report an increased risk of cerebrovascular events among hyperthyroid as well as euthyroid treated with RAI

for benign thyroid disorders. The finding of increased risk of the same magnitude in these two groups indicates that it is not solely hyperthyroidism that explains the previously noticed increased risk of cerebrovascular events after RAI. This study raises the possibility that therapy with RAI might play the most important role. Therefore, this information should perhaps be taken into consideration when advising patients with benign thyroid disease in the choice of treatment modality.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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