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Radioiodine treatment of patients with graves hyperthyroidism – What should patients be told about its effects on the eyes

Abstract

Introduction: Many studies have shown that existing eye disease (ophthalmopathy) often worsens following Radioiodine (RAI) treatment of Graves hyperthyroidism. The development of new-onset eye disease is very uncommon. However, it does occur in a few patients, and it is unclear what patients should be told when planning treatment. We addressed this problem by studying a group of well-characterized patients, 20 with no eye signs at the time of treatment and 12 with existing ophthalmopathy) seen by one observer in a single clinical setting at the time of radioiodine treatment and on long-term follow-up. **Methods:** Standard clinical observations of patients with Graves disease before and after radioiodine treatment were made. Changes in eye signs and symptoms were assessed as I) NOSPECS class, ii) Clinical Activity Score (CAS), iii) upper eyelid retraction (yes, no) and iv) Nunnery I (no extraocular muscle dysfunction or damage) and Nunery II, with eye muscle damage. Thyroid function tests were carried out, and serum thyroid antibodies, including TSH-Receptor antibody, were measured using routine methods. We also measured serum eye muscle (calsequestrin) and collagen type XIII antibodies. **Results:** Existing ophthalmopathy worsened in 5(42%) of the 12 patients, especially in female smokers, but new (*de novo*) eye disease was seen in only two of 20(10%) patients without ophthalmopathy at the time of radioiodine treatment on long term follow up, both of whom had mild disease (CAS 2, 2, NOSPECS 3, 2 with no extraocular muscle dysfunction (Nunery I), respectively). Serum TSH-Receptor antibodies increased in 50% of both groups, while orbital antibodies showed no trend in either group. **Discussion:** While the pathogenesis of Graves ophthalmopathy is still unclear, the eye disorder seems to occur following an immune reaction in the thyroid, probably as a result of the transfer of cross-reactive cytotoxic antibodies and T cells to the orbit. Radioiodine-damage to the thyroid follicular cells leads to the release of various proteins, including the main antigens involved in thyroid autoimmunity, namely thyroid peroxidase, thyroglobulin, the TSH receptor and the IgF-1R receptor, which leads to worsening of existing eye signs. While existing ophthalmopathy can usually be managed by treatment with oral or IV steroids, larger studies need to be carried out to determine the true prevalence of new eye disease and how to prevent it. **Conclusion:** Although the development of *de novo* ophthalmopathy following radioiodine is very uncommon, occurring in only 5-10% of patients, it can occur, and so it seems prudent for the managing endocrinologist to warn all patients with Graves disease, especially female smokers, of this possibility if only to avoid being accused of malpractice.

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Introduction

It is generally agreed that that the orbital inflammation and eye signs (ophthalmopathy) associated with Graves hyperthyroidism are secondary to immune reactions in the thyroid [1-3]. The main target antigens involved in the thyroid and orbital reactions of Graves disease are; thyroglobulin [4-6], thyroid peroxidase [7], the TSH-Receptor [8-12] IgF-Receptor1 (IgF-1R) [13-16] of which the latter two may be co-expressed [17-19]. Autoimmune reactions against these proteins are an important manifestation of the pathogenetic immune reactions occurring during the early stages of "Graves disease" Following Radioiodine (RAI) treatment of Graves hyperthyroidism large amounts of the proteins which are released from damaged thyroid follicular cells are targeted by infiltrating inflammatory cells and cytotoxic antibodies [20-22]. Some of the T cells and antibodies react with the same proteins in the orbital connective tissue and Extra Ocular Muscles (EOM), through the process of cross-reactivity, increasing signs of existing ophthalmopathy [23-26] or inducing new (*de novo*) eye disease [27,28].

As the orbital inflammation develops other antigens including Calsequestrin (CSQ) [29] and collagen XIII (coll-XIII) [29,30] are released from inside the Extra Ocular Muscle (EOM) fibres and orbital fibroblasts, respectively, and serum antibodies targeting these proteins may contribute to the orbital tissue damage in the longer term. Although not primary, these orbital antibodies do provide useful markers for the ophthalmopathy [31,32].

The finding that existing ophthalmopathy often worsens after RAI and that *de novo* ophthalmopathy may also occur is important in our understanding of the pathogenesis of GO and provides strong evidence that the orbital reaction is secondary to that in the thyroid and that ross reactivity is the likely mechanism. Whilst the development of new eye disease is uncommon it does occur, as described above. Here, we report a study of a group of well characterized patients with and without ophthalmopathy seen by a single observer (JW) in one clinical setting over a 10-year period.

Clinical subjects and methods

Clinical subjects: All patients with Graves hyperthyroidism who had been treated with RAI at Nepean Hospital, Penrith NSW (2004-2016) or The Thyroid Clinic at the Bays Private Hospital, Mornington VIC, over the period 2016-2022. Of these, 32 patients with Graves hyperthyroidism of whom 12, 11 females aged 38-80 (mean age 50) and one male aged 43 had active ophthalmopathy and 20 patients, 17 females aged 22-86 (mean age 50) and 3 males aged 45-70 (mean age 50) had no eye signs at the time of RAI treatment, Ophthalmopathy was defined as NOSPECS classes 2 or more [34], i.e., all patients had at least chemosis, conjunctival injection and periorbital swelling and some had inferior rectus muscle involvement (causing double vision and reduced upward gaze (NOSPECS class 4, Nunery 2 [35]. Exclusions were; age <18 or >80, hyperthyroidism due to conditions other than Graves disease, eye conditions other than thyroid eye disease or Mental health disorder other than symptoms attributable to features of the Graves hyperthyroidism itself, such as irritability anxiety or heat intolerance. Inclusions were; patients with Graves disease with or without ophthalmopathy (eye signs) who were treated with RAI only.

All patients with ophthalmopathy had moderately severe or severe eye disease which was active, quantified as a Clinical Activity Score (CAS) of Moritz et al. [36] of 4 or more. Serum antibody results were obtained from their files; eye muscle and collagen XIII antibody tests had been carried out in the context of their routine clinical management, and the patients' smoking status (yes, no) was obtained by questioning during their initial clinical visit. Two patients with active ophthalmopathy and 3 with no eye signs received two RAI treatments each and are shown in the (Tables) as separate individuals The Nepean Blue Mountains Human Ethics Committee approved the study. Because the study was retrospective and anonymous consent forms were not needed.

Methods

Enzyme-linked immunosorbent assay: The method has been described in previous publications from this laboratory [32,37,38]. The main antibodies proposed are those targeting i) the flavoprotein (Fp) subunit of mitochondrial succinate dehydrogenase; ii) G2s, shown to be a fragment of the FOX-P1 transcription factor; iii) the calcium-binding protein Calsequestrin (CSQ); and iv) collagen XIII (COLL XIII), a connective tissue antigen expressed in the orbital fibroblast cell membranes. Tests were performed in triplicate in 96 well plates. The optimal concentrations of purified calsequestrin, Fp, G2s and COLL XIII were found, in preliminary assays, to be one pg/ml (picogram/ml) for each protein, and optimal serum dilution was 1/50 for CSQ, Fp2, G2S and 1/25 for COLL XIII. The second antibody was an alkaline phosphatase· labelled goat anti-human IgG diluted 1/4000. We used Phosphate-Buffered Saline (PBS) as a control instead of an antigen, serum, or secondary antibody. Results were expressed as Optical Density (OD) at 410 nm and a positive test taken as an OD > mean + 2SD for a panel of age and sex-matched healthy subjects. Commercial Pathology Laboratories performed serum TSH and TSH-Receptor (TSHR) tests in Sydney and Melbourne.

Statistical analysis

Statistical differences between patient groups were determined using the student t-test. For all analyses, a P value of <0.05 was considered to be significant. The GraphPad Prism 8 statistical package was used for the analyses.

Results

Twenty-eight patients underwent 33 RAI treatments over the period 2004-2022. As seen in (Table 1) only 2 of the 20 patients (23 treatments) who had no eye signs at the time of RAI treatment developed *de* novo (new) ophthalmopathy, whereas 5(42%) of the 12 patients who had ophthalmopathy at the time of treatment, had worsening of their eye signs within 1 to 15 months after the treatment, Three of these 5 patients were current smokers.

Table 1: Summary of change in existing ophthalmopathy or the development of new (*de novo*) ophthalmopathy following radioiodine treatment in patients with Graves hyperthyroidism.

Patients/treatments (n=32)[1]	Change in ophthalmopathy following radioiodine treatment			Development of new ophthalmopathy following radioiodine treatment
	Worse	Better	No change	
Ophthalmopathy at the time of radioiodine (n=12)	5(42%)	5(42%)	2(16%)	
No ophthalmopathy at the time of radioiodine (n=20)	18(90%)			2(10%)

[1]28 patients underwent 33 radioiodine treatments.

Details of the 12 patients (2 of whom had two treatments) with existing ophthalmopathy at the time of RAI treatment are shown below along with change in parameters of their ophthalmopathy after treatment in (Table 2). Worsening of eye signs occurred in 3 females (patients 1, 2 ,12) all of whom were smokers and one of whom (no, 1) had eye muscle damage. The dose of RAI measured as mCi or mbeq varied or was not known but the average dose was approx. 12-15 mCi, with no apparent association with changes in eye signs.

Next, we documented the outcomes for the 20 patients (3 of whom had 2 treatments) with no ophthalmopathy at the time of RAI treatment. The results are summarised in (Table 3) below. There were no particular features of the two patients (no. 3 and 17) who developed new (*de novo*) ophthalmopathy after RAI.

Table 2: Change in existing eye signs following radioiodine treatment of patients with Graves hyperthyroidism.

Case no.[1]	Age/Sex	RAI dose (mCi/mbeq)	Cigs	Ophthalmopathy features at time of treatment[2]				Effect of radioiodine treatment on eye signs		
				NOSPECS class	CAS	UER	Nunery (1,2)	No Change	Better	Worse
1a	61/F	488	Yes	2	2	N	1			X
1b		600	Yes	2	2	Y	2			X
2	41/F	600	Yes	2	4	Y				X
3	43/M	15	Yes	4	5	Y	2		X	
4	42/F	10	No	2	1	Y	1			X (lid only)
5a	40/F	?	No	5	4	Y	2		X	
5b		543	No	5	4	Y	2		X	
6	38/F	400		6	2	Y	1		X	
7	59/F	452	No	1	1	Y	1		X	
8	? /F	?		3	2	N	1	?		
9	45/F	452								
10	80/F	?	No	2	2	Y	1		X	
11	63/F	15	No	2	2	Y	1		X	
12	40/F	?	Yes	2	2	Y	1			X

[1]Patients 1 and 5 underwent two treatments (a,b); [2]NOSPECS = Class of ophthalmopathy [34], CAS = Clinical Activity Score, [36], UER = Upper Eyelid Retraction, Nunery 1, with no eye muscle involvement, 2 with eye muscle involvement [35].

Table 3: Eye signs following radioiodine treatment in patients with Graves hyperthyroidism who had no associated ophthalmopathy initally.

Case no.[1]	Age/Sex	dose (mCi) or mBeq	Cigs	Ophthalmopathy features at 4-8 weeks following treatment[2]			
				NOSPECS	CAS	UER	Nunery
1a	31/F	12.5	No	0	o	o	n/a
1b		15	No	o	o	o	n/a
2	45/M	165	Yes	o	0	0	n/a
3	63/F	20	No	3	2	Yes0	1
4	48/F	11	No	0	0	0	n/a
5	? /M	?	?	0	0	0	n/a
6	62/F	?	No	0	0	0	n/a
7	72/F	?	No	0	0	0	n/a
8a	57/F	12	No	0	0	0	n/a
8b	?	12.3	No	0	0	0	n/a
9a	43/F	12	No	0	0	0	n/a
9b	?	?	No	0	0	0	n/a
10	86/F	11.7	No	0	0	0	n/a
11	80/F	12.9	No	0	0	0	n/a
12	63/F	596	?	0	0	0	n/a
13	80/M	?	No	0	0	0	n/a
14	52/F	12	No	0	0	0	n/a
15	49/F	?	No	0	0	0	n/a
16	70/M	?	Yes	9	0	0	n/a
17	22/F	12	No	2	2	1	1

[1]17 patients underwent 33 radioiodine treatments; [2] NOSPECS = Class of ophthalmopathy [34], CAS = Clinical Activity Score, [36], UER = Upper Eyelid Retraction, Nunery 1, with no eye muscle involvement, 2 with eye muscle involvement [35].

We next addressed possible changes in TSH R antibody levels in Graves patients following RAI treatment. The results for the 26 patients who had this antibody measured are shown below in Table 4. There were no significant differences between the 4 groups namely, increased, no change, decreased and decreased then increased.

Finally, we addressed whether change in levels of orbital antibodies following RAI in the 5 patients in whom these antibodies were measured correlated with change in, or development of, eye changes. As seen in (Table 5) below there was no clear relationship between change in levels of the two orbital antibodies measured and ophthalmopathy.

Table 4: Change in serum TSH-Receptor antibody levels following radioiodine treatment in patients with Graves hyperthyroidism with or without ophthalmopathy.

N	TSH-R Ab levels increased	No change In TSH-R Ab levels	TSH-R Ab levels decreased	Decreased	Decreased then increased
No ophthalmopathy at time of radioiodine treatment					
16	8(50%)	7(44%)	1(6%)		
Ophthalmopathy at the time of radioiodine or *de novo* after radioiodine					
10	5(50%)	3(30%)		0	2(20%)
Totals 26	13(50%)	10(38%)		1(4%)	2(7%)

Table 5: Serum levels of orbital antibodies before and after radioiodine treatment in 5 patients with Graves hyperthyroidism and ophthalmopathy.

	Orbital antibody		
	Calsequestrin	Collagen-XIII	Ophthalmopathy[1]
1	Slightly down	No change	Yes
2	Increased to high then stable	Very increased to stable	Yes
3	Increased to very high then variable	Increased to high then stayed high	Yes
4	No change/negative always	No change/negative always	Yes
5	No change	No change/slightly increased	Yes

[1]at time of radioiodine (*) or *de novo* following radioiodine (**).

Discussion

The proportion of Graves patients treated with RAI is very high in the US (75%) but very low (11%) in Australia, for reasons that one can speculate upon. So, it is important to document the proportion of patients with no ophthalmopathy at the time of RAI who develop the eye disease within a few weeks of treatment.

To summarise the findings from our small study; we show that existing ophthalmopathy worsened in 5(42%) of the 12 patients after RAI, especially in female smokers, whereas new (*de novo*) eye disease was seen in only two of 20(10%) patients without ophthalmopathy at the time of radioiodine treatment, both of whom had mild disease Serum TSH-Receptor antibodies increased in 50% of both groups, while orbital antibodies showed no trend in either group.

The worsening of ophthalmopathy following RAI is presumed to be due to the increased release of thyroid and orbital tissue shared antigens leading to increased orbital inflammation. On the other hand, eye signs are expected to decrease in the long term because the thyroid and orbital tissue shared proteins are eventually destroyed by the radiation. Although we were unable to confirm this since long term follow up was not possible.

We have shown recently that patients with Graves diseases who smoke have higher blood levels of antibodies targeting orbital antigens than nonsmokers [32], the first evidence that smoking has a direct effect on the immune reactions in the orbit this confirming the hypothesis that ophthalmopathy is secondary to the thyroid autoimmunity through cross reactivity against thyroid and orbital shared autoantigens, which is worse in smokers [38-41]. Endocrinologists need to be concerned about the effects of smoking, which may be much greater than we realise.

Thyroid associations management guidelines

Recommendations of the American Thyroid Association (ATA) [42], the American Association of Clinical Endocrinologists [AACE] [43] and the European EUGOGO Group [44] regarding the ophthalmopathy which occurs in association with hyperthyroidism in 50% of patients with Graves disease provide guidelines for its management and the possible effects of radiation on the eyes. However, it is noteworthy that none of the three associations have mandated, or even suggested, that endocrinologists should warn patients without eye disease of the unlikely possibility of developing *de novo* ophthalmopathy. Smokers should be warned because we know they are at risk of developing ophthalmopathy, as shown in our study.

Treatment of graves hyperthyroidism

If treatment of Graves hyperthyroidism with RAI is considered too dangerous for routine use many would choose long term antithyroid medication to be the best currently available treatment of this common thyroid disorder. However, RAI has been described by some as “the best treatment floor any disease” we should not exclude this “magic bullet” from future discussion. Total thyroidectomy is another classical way of treating Graves hyperthyroidism but the sides effects of surgery namely’ voice changes, recurrent laryngeal nerve damage hypothyroidism, hypoparathyroidism, neck swelling and the need to stay in hospital for at least two days post-surgery will always be a problem. Total thyroid radiofrequency ablation might be a future approach, ophthalmopathy perhaps carried out a well-designed AI robots, such as those used to deal with prostate enlargement and cancer.

Limitations of the study

The study was retrospective, the case numbers were small and some of the clinical data, such as the dose of RAI used, were not available. On the other hand, the fact that there was only one clinical observer who carried out all tests including thyroid ultrasound, and that the study was carried out at only two sites, were strong points in favor of our approach to address this important issue.

Conclusion

Although studies, including our own, show that the development of new eye disease is very uncommon in Graves patients treated with RAI it does, seem prudent to warn all patients about this possibility. We therefore advise endocrinologists that, in order to avoid being accused of harming their patients, they should warn their patients about this uncommon (but not rare) event, and document this in the case file and correspondence with their GP.

Declarations

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