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ORIGINAL ARTICLE

An Audit on Thyroid Scintigraphy Scan Requests in Benign Thyroid Disease

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Background

Thyroid scintigraphy has a useful role in the assessment of the thyrotoxic patient, particularly when thyrotoxicosis coexists with thyroid nodularity and when TSH- receptor antibody (TRAB) is negative. The aim of this audit was to assess the indication for thyroid scintigraphy in the assessment of patients locally, with reference to the European Thyroid Association (ETA) and National Institute for Health and Care Excellence (NICE) guidelines.

Methods

All scintigraphy scans carried out in adult patients with benign thyroid disease at Mater Dei Hospital in Malta, between January 2019 to December 2021, were analysed. The indications for the investigation and the imaging results were assessed using the hospital's electronic records, as were the thyroid function tests, TRAB levels, and thyroid ultrasound scans if available.

Results

In 55.95% of thyrotoxic subjects, there was no valid indication for thyroid scintigraphy, according to the ETA and NICE guidelines. 37.96% of these patients inappropriately referred for scintigraphy did not have a TRAB level checked prior to the scan date whilst 20.37% had a positive TRAB and no known thyroid nodules. 10.18% of scans were inappropriately ordered in euthyroid patients with thyroid nodules or euthyroid hyperthyroxinaemia.

Conclusion

TRAB levels should be checked in new-onset thyrotoxicosis. Thyroid scintigraphy is useful in the differential diagnosis of the thyrotoxic patient when there are co-existing thyroid nodules, especially if TRAB is negative. It is not recommended in the thyrotoxic patient with a positive TRAB and no known thyroid nodules or in the assessment of euthyroid patients with thyroid nodules.

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Thyroid scintigraphy scanning is a useful imaging modality, which is widely used in the investigation of thyrotoxicosis. Depending on the pattern of uptake, it can help to distinguish between Grave's disease (diffuse uptake), toxic adenoma (increased uptake at the site of the nodule with suppressed uptake in the surrounding thyroid tissue), toxic multinodular goitre (multiple foci of variably increased tracer uptake, with suppression of the remaining thyroid tissue) and thyroiditis (reduced or absent uptake).

Although it is a useful adjunctive test in the investigation of thyrotoxicosis, it is not necessarily a first-line or routine test and incurs additional costs to healthcare systems. According to the 2018 European Thyroid Association (ETA) guideline for the management of Graves' hyperthyroidism, the initial assessment should include measurement of the TSH-receptor antibody and an ultrasound scan of the thyroid. Thyroid scintigraphy scanning is suggested only when thyroid nodularity coexists with hyperthyroidism, and prior to radioactive iodine therapy.[1] NICE guidelines also recommend measuring TSH-receptor antibodies in all patients with thyrotoxicosis but suggest an ultrasound only when thyroid nodules are suspected clinically and suggest thyroid scintigraphy if the TSH-receptor antibody is negative.[2]

The aim of this audit was to assess the indications for thyroid scintigraphy scans being performed locally in adult patients with benign thyroid disease, in order to determine whether they comply with the European Thyroid Association guidelines and to assess whether they were necessary to establish the diagnosis and influence management.

MATERIALS AND METHODS

All thyroid scintigraphy scans carried out in adult patients (16 years of age and over) with benign thyroid disease at Mater Dei Hospital, Malta from January 2019 to December 2021 were included. These were analysed using the hospital's electronic records (including Centricity Clinical Viewer and iSOFT Clinical Manager) for imaging and blood investigations. Ethical approval was obtained from the local regulatory committee. The indication and actual result of each radio-isotope scan was reviewed for each patient. In addition, thyroid function tests, TSH-receptor antibodies, and thyroid ultrasound scans were reviewed for each of the patients, if performed prior to the scintigraphy scan.

RESULTS

A total of 216 thyroid scintigraphy scans were performed on adult patients over a three-year period between January 2019 and December 2021. The mean age of our study population was 60.5 years (range: 19-94 years) with a female predominance (66.6%). The female average age was 59.06 (range 19-90) and the male average age was 63.66 years old (range 26-94). 71.8% (n=155 patients) of the population had overt thyrotoxicosis, and 17.59% (n=38 patients) of the population had subclinical hyperthyroidism. 10.18% (n=22 patients) of the population were euthyroid, whilst 1 patient (0.46%) had no thyroid function test available on iSOFT. 31.48% of the study population had positive TSH-receptor antibodies whilst a TSH-receptor Ab was not available in 26.38% of the population.

The 2018 ETA Guideline recommends scintigraphy of the thyroid in thyrotoxic patients with co-existing thyroid nodularity on imaging.[1] 126 patients of the study population who were being evaluated for overt or subclinical thyrotoxicosis (65.28%) satisfied this criterion (Table 1).

The 2019 NICE Guideline recommends scintigraphy of the thyroid gland in TSH-receptor Ab-negative thyrotoxic patients.[2] Only 85 patients (44% of the thyrotoxic sub-population) fulfilled this criterion. Analysis of the data pertaining to the remaining 108 patients with thyrotoxicosis (55.95%) inappropriately referred for scintigraphy, revealed that 41 patients (37.96%) did not have a TSH-receptor antibody sampled prior to the scintigraphy scan, while 22 patients (20.37%) had a positive TSH-receptor antibody with no known thyroid nodules (Table 1).

In our cohort, thyroid scintigraphy scans added significant information to narrow the differential diagnosis of thyrotoxicosis in patients with negative TSH-receptor antibody status and in those with positive TSH-receptor antibody status associated with thyroid nodules.

In those patients with positive TSH-receptor antibody status and no known thyroid nodules, thyroid scintigraphy scans altered the diagnosis in 2 patients out of this sample (i.e. 2 out of 22 patients). One of these two patients had a thyroid scintigraphy scan suggestive of a toxic adenoma and an ultrasound performed later confirmed the presence of a thyroid nodule whilst the other patient had a scintigraphy scan indicative of thyroiditis.

Table 5 Thyrotoxic patient cohort and their respective TRAB, US and Scintigraphy findings. The scintigraphy cases highlighted in green are the ones that are recommended as per the 2018 ETA guideline. The scintigraphy cases highlighted in yellow are the ones that are recommended as per the 2019 NICE guideline. The scintigraphy cases highlighted in grey are the ones that are recommended as per both the 2018 ETA and the 2019 NICE guidelines.

TRAB	Nodules on US	Diffuse Uptake	Uptake suggestive of TMNG	Uptake suggestive of TA	Reduced / Absent uptake	Normal uptake	Ectopic thyroid tissue
Positive	No	4			1	3	
Positive	N/A	11		1		2	
Positive	Yes	26	6	5		9	
Negative	No	8	1		3	5	
Negative	N/A	3		1	4	5	
Negative	Yes	16	9	12	3	15	
Not available	No						
Not available	N/A	7		1	2	5	
Not available	Yes	10	2	8	1	4	

TRAB: TSH-receptor antibody; US: ultrasound; TMNG: Toxic multinodular goitre; TA: toxic adenoma

39.09% of thyrotoxic subjects with diffuse and normal thyroid uptake had a negative TSH-receptor Ab status.

Toxic adenomas were more common in females in this study. Using the chi-square test, a p-value of 0.048 was achieved (< 0.05).

In the euthyroid cohort (n=22 patients), the two most common reasons for ordering thyroid scintigraphy scans were:

1. to assess whether a nodule is hot, cold, or warm (54.5%) and
2. in patients with euthyroid hyperthyroxinaemia (31.8%).

In one euthyroid individual, a thyroid scintigraphy scan was requested to assess for ectopic thyroid tissue as a previous ultrasound of the neck had revealed a soft tissue nodule of uncertain origin.

DISCUSSION

Thyroid scintigraphy plays an important role in the assessment of the thyrotoxic patient in selected cases. It is based on the thyroid's ability to take up iodine via the sodium-iodide symporter. Technetium-99m (99mTc) is an analogue of iodine which is also transported to thyroid cells by means of the sodium-iodide symporter, allowing its use in thyroid scintigraphy in order to visualize the distribution of active thyroid tissue.[3]

According to the 2018 European Thyroid Association (ETA) guideline for the management of Graves' hyperthyroidism, thyroid scintigraphy scanning is suggested only when thyroid nodularity coexists with hyperthyroidism, and prior to radioactive iodine therapy.[1] The 2019 NICE Thyroid Disease: Assessment and Management guideline recommends measuring TSH-receptor antibodies in all patients with thyrotoxicosis but suggests an ultrasound only when thyroid nodules are suspected clinically and suggests thyroid scintigraphy if the TSH-receptor antibody is negative.[2]

Based on the results obtained in this audit, thyroid scintigraphy scans were particularly useful in establishing a diagnosis in those individuals with thyrotoxicosis and co-existent thyroid nodularity, especially when the TSH-receptor antibody was negative. In this audit, thyroid scintigraphy was not found to add any relevant information in thyrotoxic patients with a positive TSH-receptor antibody (TRAB) and no known thyroid nodules.

The presence of Graves' disease does not necessarily exclude the presence of thyroid nodules. In this audit, 46 patients (23.8% of the cohort with thyrotoxicosis) had positive TSH-receptor antibody status and co-existent thyroid nodules. 13% (n=6 patients) of this patient cohort had a thyroid scintigraphy pattern suggestive of toxic multinodular goitre whereas 10.8% (n=5 patients) had a thyroid scintigraphy pattern suggestive of a toxic adenoma. This is important, as by distinguishing Graves from other causes of thyrotoxicosis, scintigraphy will influence management in the long term. Patients with a toxic multinodular goitre or toxic adenoma usually should ideally be treated with a definitive option such as

surgery or radioactive iodine therapy if feasible, since long-term antithyroid drugs (ATDs) would otherwise be necessary as maintenance to control thyrotoxicosis. On the other hand, a 12 to 18-month course of ATDs is an established first-line approach in most cases of Graves' disease with tapering of ATDs then attempted based on TFTs and TRAB levels with subsequent monitoring for relapse.[1,4]

The use of TSH-receptor antibody in patients presenting with thyrotoxicosis is a useful and cost-effective measure which, if elevated, often leads to a rapid and accurate diagnosis of Graves' disease. The latter is reflected in the current guidelines. However, a study by Angell et al identified the presence of positive TSH-receptor antibody in thyrotoxic patients without Graves' disease.[5] Albeit rare, the above clinical possibility highlights that scintigraphy may have a role in patients presenting without pathognomonic evidence of Graves' disease and minimally elevated TSH receptor antibody levels.

One instance wherein thyroid scintigraphy may be useful in the initial assessment of a thyrotoxic patient is when an acute form of thyroiditis is suspected, especially silent thyroiditis or postpartum thyroiditis. In addition to the clinical presentation and thyroid function tests, scintigraphy scans play a complementary role in such instances as it may differentiate thyroiditis from other forms of thyrotoxicosis, with reduced uptake expected in cases of thyroiditis.[6]

In this audit, it was noted that 54.5% of euthyroid subjects, (i.e., 5.6% of the total study cohort), underwent thyroid scintigraphy in order to assess the functionality of a thyroid nodule. Although thyroid scintigraphy is an effective imaging method for assessing the functional aspect of a thyroid nodule, an ultrasound performed by an experienced ultrasonographer is the gold standard for the structural assessment of a thyroid nodule. In the assessment of thyroid nodules, thyroid scintigraphy should only be performed when the TSH level is suppressed in order to assess whether a nodule is 'hot', 'cold', or 'warm'. The presence of a cold nodule in Graves' disease carries a higher risk of malignancy than a cold nodule in the absence of autoimmune thyroid disease.[7] In these instances, information obtained from scintigraphy can be used in addition to careful assessment of the nodular sonographic features and fine-needle aspiration in order to better characterize and stratify the risk of thyroid nodules in patients with Graves' disease, with priority given to FNA sampling of cold nodules. However, in the euthyroid patient, thyroid scintigraphy is not indicated and assessment for risk of malignancy should be performed via ultrasound with FNA sampling being dictated based on the nodule's size and characteristics on ultrasound.[8]

In this audit, we also observed that a number of patients with diffuse homogenous uptake on their

SUMMARY BOX

What is already known about this subject?

- Checking serum TSH-receptor antibody (TRAB) is a cost-effective investigation in the diagnosis of Graves' disease and is recommended in the assessment of new-onset thyrotoxicosis.
- Thyroid scintigraphy is a useful adjunctive investigation in the assessment of the patient presenting with thyrotoxicosis when there is coexisting thyroid nodularity, as recommended by the European Thyroid Association (ETA) guidelines.
- Thyroid scintigraphy is recommended by the National Institute of Clinical Excellence (NICE) in the assessment of the patient presenting with thyrotoxicosis when TRAB is negative.

What are the new findings?

- In this audit, 55.95% of thyroid scintigraphy scans ordered during investigation of thyrotoxicosis at Mater Dei Hospital in Malta between the beginning of 2019 and the end of 2021 were not indicated according to the ETA and NICE guidelines, where 37.96% of this patient cohort inappropriately referred for scintigraphy did not have a TRAB level checked prior to the scan whilst 20.37% had a positive TRAB with no known thyroid nodules.
- 5% of euthyroid subjects (5.6% of the total study cohort) were inappropriately referred for thyroid scintigraphy to assess the functionality of a thyroid nodule, though in euthyroid patients the risk of malignancy of thyroid nodules should be evaluated based on ultrasound characteristics followed by fine needle aspiration (FNA) if necessary.
- Increased awareness on the indications for thyroid scintigraphy is likely to reduce unnecessary costs and waiting times by prioritising this investigation for those patients in whom it is likely to influence management namely in thyrotoxic individuals with co-existing thyroid nodularity, particularly if TRAB is negative.

thyroid scintigraphy scans had a negative TSH-receptor antibody status. It is possible that some of these patients had already been started on ATDs prior to the TRAB levels being checked. Since effective treatment with ATDs is associated with a lowering of TRAB titres[1], a proportion of this cohort might have exhibited TRAB positivity had this been checked earlier. Autoantibody-negative Graves' disease is a subject of debate as Graves' disease is proposed to be a systemic disease.[9] Studies have revealed that autoantibody-negative Graves' disease does exist, albeit rare.[10] This may occur for a number of reasons. Scatti Regàs A et al suggest that the tests for the detection of TSH receptor antibody may not be sensitive enough to detect low antibody concentrations.[11]

Another postulated explanation is that patients might exhibit TSH receptor mutations leading to chronic TSH receptor stimulation. The latter leads to a similar clinical and biochemical picture to that seen in Graves' disease, but without any detectable TSH receptor antibody.[12]

Yet another potential explanation for the occurrence of TSH-receptor antibody negative Graves' disease, is that the production of TSH-receptor antibody may be restricted solely to the thyroid. This hypothesis is based upon evidence that lymphocytes isolated from the thyroid of a patient with TSH receptor antibody seronegative autoimmune thyroiditis, could produce anti-thyroid antibodies,[11, 13-14] despite undetectable levels in serum.

CONCLUSION

Thyroid scintigraphy plays an important role in the assessment of the thyrotoxic patient and is particularly useful in patients who also have thyroid nodules. All patients presenting with new-onset thyrotoxicosis should have blood sampled for TSH-receptor antibody levels. Most patients presenting with thyrotoxicosis with positive TSH-receptor antibody levels will have Graves' disease. In the absence of thyroid nodules, a thyroid scintigraphy scan is unnecessary in thyrotoxic patients. However, if thyroid nodularity coexists, a thyroid scintigraphy scan is indicated to help distinguish between Graves' disease, toxic multinodular goitre and toxic adenoma. A case can be made for ordering a thyroid scintigraphy scan if acute thyroiditis is suspected based on the clinical presentation since the pattern of reduced uptake is diagnostic. Euthyroid or hypothyroid patients found to have thyroid nodules do not benefit from thyroid scintigraphy and should instead be investigated via an ultrasound scan of the thyroid. A decision to proceed with US-guided FNA should be guided by the patient's thyroid ultrasound characteristics. This audit revealed that a number of thyroid scintigraphy scans performed locally between 2019 and 2021 were not necessary for accurate diagnosis and management. Through this audit, we hope to raise awareness that thyroid scintigraphy scans should no longer be ordered to assess thyroid nodules in euthyroid or hypothyroid patients and is also unnecessary in patients with clinical and biochemical evidence of TSH-receptor antibody positive Graves' disease if thyroid nodularity does not coexist. Such a diagnostic approach will help reduce unnecessary costs and optimise the allocation of healthcare resources.

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