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Assessment of Association of Thyroid Associated Ophthalmopathy in Post Thyroidectomy Patients

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Abstract
Thyroid associated Ophthalmopathy is an autoimmune inflammatory orbital disorder most commonly associated with Graves' disease (GD) which includes spectrum of severity from dry eye symptoms to autoimmune optic neuritis leading to loss of vision. There are very few studies in the literature which have compared association of thyroid associated ophthalmopathy in post thyroidectomy patients. A retrospective observational study in which patients who underwent thyroidectomy between May 2018 and May 2022 were included by reviewing the medical records. Based on clinical examination using NOSPECS criteria and Clinical activity score (CAS) patients were placed into active disease group and non-active disease group. Dry eye was also investigated among these patients. A total of 68 patients who underwent thyroidectomy were contacted. The mean age of the subjects was 46.3 years. 66 patients were females and 2 were males. On ophthalmic examination active TAO [clinical activity score (CAS)=3] diagnosed in 3 (4.4%) patients, among which 2 patients had upper eyelid retraction of both eyes and 1 patient had upper eyelid retraction and right eye proptosis. 06 (8.8%) patients who underwent the TSH receptor autoantibody test, showed positive findings. 11 (16.2%) patients were diagnosed to have dry eye disease. Ophthalmopathy may develop in patients after thyroid surgeries for thyroid diseases. We recommend that all post thyroidectomy patients should undergo eye examination for TAO in follow up period.

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Key Words
Opthalmopathy, graves' disease, thyroidectomy

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INTRODUCTION

Thyroid associated Ophthalmopathy is an autoimmune inflammatory orbital disorder most commonly associated with Graves' disease (GD) which includes spectrum of severity from dry eye symptoms to autoimmune optic neuritis leading to loss of vision[1]. Dry eyes symptoms such as grittiness, itching, or burning can be related to problems with thyroid gland. Sometimes they may be the first sign of a thyroid disease[2]. According to Tanda[3], one-third of 346 GD patients at a single centre presented with ophthalmic manifestations at their initial visit and nearly 20% of patients who did not present Graves' Ophthalmopathy (GO) at their initial visit, develop Ophthalmopathy during the follow-up period. Although the pathophysiology of this mechanism is not fully understood, the thyroid-stimulating hormone (TSH) receptor, which is present in thyroid follicular cells and orbital connective tissue, might act as a common autoantigen[1,2]. TSH receptor autoantibodies have been associated with the severity or activity of GO[4,5]. In terms of the association between TAO, GD and thyroid cancer, patients with GD have a higher incidence of papillary thyroid cancer (PTC) than those without GD, which may be due to the higher thyroid hormone activity in GD patients than in the normal population[6]. However, the incidence of newly diagnosed TAO after thyroid surgery is not well known. Furthermore, due to its rarity, little is known about preoperative factors that can predict the development of TAO after thyroid surgery. There are very few studies in the literature which have compared association of thyroid associated ophthalmopathy in post thyroidectomy patients.

We assessed the incidence of newly developed TAO after thyroid surgery in a retrospective cohort study conducted in a single tertiary centre in south Bihar.

MATERIALS AND METHODS

It was a retrospective observational study in which the medical records of patients, who had undergone thyroidectomy between May 2018 to May 2022. were reviewed and structured telephonic questionnaires (based on clinical activity score) were administered. If any positive answer was found on questionnaire, it was followed by clinical examination by an Ophthalmologist to search for the spectrum of TAO in these patients. If the patient had any positive finding on ophthalmological examination then that patient was kept in active disease group. The patients who did not have any positive finding on ophthalmological examination were kept in non-active disease group. Patients with connective tissue disorder, previous pre-existing eye disease and inadequate contact details were excluded from the study. Diagnosis of TAO was made by one ophthalmologist based on the NOSPECS criteria and Clinical activity score. Dry eye was also investigated among these patients. A value<10mm on schirmer test was diagnosed as dry eye disease. Age, sex, treatment after thyroidectomy and relationship between the surgery and ocular symptoms were also reported.

Schirmer Test: The Schirmer I test measures total tear secretion, including reflex and basal tears. Without instilling anesthetic drops, the Schirmer strips are inserted into the lower conjunctival sac at the junction of lateral one-third and medial two third, avoiding contact with the cornea and the length of wetting strips is recorded in millimeters after 5 minutes. Normal mean test values range from 8 mm to 33 mm, but an accepted normal value is greater than 10 mm[7,8]. A variation is the Schirmer II test, which uses topical anesthesia and only measures reflex tears.

RESULTS AND DISCUSSIONS

A total of 68 patients fulfilling our inclusion criteria were contacted. The mean age of the subjects was 46.3 years. 66 patients were females and 2 were males. Out of these 9 patients had under gone total thyroidectomy, 30 patients underwent subtotal thyroidectomy, 17 underwent hemithyroidectomy and 12 patients had lobectomy done. On telephonic questionnaires, 34 patients gave positive response and were called for ophthalmological examination. Out of these only 26 patients consented and reported for clinical examination by an ophthalmologist. All 26 patients were females with mean age of 34.2 years. Out of these 26 patients, 2 had under gone total thyroidectomy, 18 patients under went subtotal thyroidectomy, 4 underwent hemithyroidectomy and 2 patients had lobectomy done.

The ophthalmic manifestations varied among cases, with active TAO [clinical activity score (CAS)=3] diagnosed in three patients, among which 2 patients had upper eyelid retraction of both eyes and 1 patient had upper eyelid retraction and right eye proptosis. Except for two patients who were in the hypothyroid state, all other patients were in the euthyroid state. Six patients of 26 patients who underwent the TSH receptor autoantibody test, showed positive findings. 11 patients were diagnosed to have dry eye disease (<10mm wetting on schirmer test).

Graves' disease is an organ-specific autoimmune disease that causes hyperthyroidism via the production of TSH receptor auto antibodies which stimulate the thyroid gland. Graves' disease is known to have a genetic-environmental etiology. Due to its ability to stimulate the growth of thyroid nodules, it may be accompanied by a colloid goiter, autoimmune lymphocytic disease, thyroid osteoarthritic changes, and hyperplastic adenomatous tissue[1]. It is common to detect Graves' disease in patients with thyroid

Table 1: Clinical activity score[9]

GO activity (CAS)	
1	Spontaneous retrobulbar pain
2	Pain on attempted upward or downward gaze
3	Redness of eyelids
4	Redness of conjunctiva
5	Swelling of caruncle or plica
6	Swelling of eyelids
7	Swelling of conjunctiva (chemosis)

Table 2: TAO Eye changes classification-NOSPECS[9]

Class	Grade	Criteria
1		No physical signs or symptoms Only signs (limited to upper lid retraction, stare, and lid lag)
2		Soft tissue involvement (with symptoms and signs)
	0	Absent
	a	a Minimal
	b	Moderate
	c	Marked
3		Proptosis ≥3 mm above upper normal limit
	0	0 Absent
	a	a 3-4 mm increase over upper normal
	b	b 5-7 mm increase
	c	c ≥8 mm increase
4		Extraocular muscle involvement
		Absent
	a	Limitation of motion extremes of gaze
	b	Evident restriction of motion
	c	Fixation of a globe or globes
5		Corneal involvement
		0 Absent
	a	Stippling of cornea
	b	Ulceration
	c	Clouding, necrosis, perforation
6		Sight loss (optic nerve involvement)
	0	Absent
	a	Disc pallor or visual field deffect., vision 20/20-20/60
	b	Same as 6a, but vision 20/70-20/200
	c	Blindness, i.e., failure to perceive light, vision < 20/200

Table 3: Types of Surgical procedure

Surgery	Number of patients
Total thyroidectomy	2 (7.7 %)
Sub-total thyroidectomy	18 (69.2 %)
Hemi thyoidectomy	4 (15.4 %)
Lobectomy	2 (7.7 %)

Table 4: Clinical findings among reported patients

Clinical manifestations	Number of patients
Bilateral/ Unilateral Upper eyelid retraction	3 (11.5 %)
Bilateral Proptosis	1 (3.8 %)
Dry eye	10 (38.5 %)
Nil finding	12 (46. 2 %)

cancer clinically, but cases of Graves' disease recurrence after partial thyroidectomy for thyroid cancer are very rare.

We examined 26 patients post thyroidectomy and found 3 cases of patients who developed TAO after thyroidectomy either for thyroid cancer or a benign mass of the thyroid. Six patients showed abnormalities in TSH receptor autoantibody tests at the time of examination. The three patients who had developed TAO after thyroidectomy were also among these six patients. Menconi[10] compared overall improvement of Graves' orbitopathy between near-total thyroidectomy and total thyroid ablation groups, reporting better outcomes of orbitopathy in the total thyroidectomy group. Winsa[11] compared TSH receptor autoantibody levels and eye involvement between subtotal thyroidectomy and total thyroidectomy and found that those characteristics benefitted from total rather than subtotal thyroidectomy. Our study also showed occurrence of TAO more among subtotal or hemi thyroidectomy compared to patients undergoing total thyroidectomy. This supports the hypothesis that minimizing the remnant thyroid tissue may be beneficial for eye involvement through the removal of shared antigens and autoreactive T-lymphocytes.

Although the mechanisms through which TAO developed in these patients were unclear, we suggest several possibilities. In cases of euthyroid status, TAO development may be related to the presence of thyroid tissue that remains after thyroidectomy. Yoon[12] performed a study on five TAO patients with thyroid cancer who tested positive for Thyrotropin Binding Inhibiting Immunoglobulines [TBII] yet showed normal thyroid function, suggesting that TAO may develop due to systemic autoimmunity and may not be induced by hyperthyroidism. Case reports of euthyroid

TAO several decades ago also describe patients with ocular signs of TAO and normal thyroid function without previous history of hyperthyroidism[13].

Considering that ophthalmopathy and dry eye occurred after thyroidectomy in our cases, ophthalmopathy may be related to the thyroidectomy itself. Several previous cases have shown the development of GD shortly after thyroid cancer surgery[12,13]. Although the mechanism for GD development after partial thyroidectomy is unclear, several hypotheses have been suggested. The first hypothesis is that the operation destroys thyroid cells, which may increase TSH receptor expression and thereby lead to GD[13]. A second hypothesis is that the operation causes postoperative GD by inducing an immune system abnormality, such as the stimulation of the antigen-presenting cells that control the activation of suppressor or regulatory cells. A third hypothesis is that the stress from general anesthesia and surgery affects the patients physically and mentally, thereby causing neuroendocrine fluctuations that disrupt immunological homeostasis. One final hypothesis is that postoperative bacterial and viral infections increase the number of CD5+ B cells, which stimulate the TSH receptor antibodies and thus contribute to GD[12].

Patients with thyroid disorders suffer from exophthalmos that affects the soft tissues of the eye leading to their expansion[14]. Exophthalmos leads to lagophthalmos. This subsequently disturbs the ocular surface and elevates the tear evaporation rate as well as tear hyperosmolarity[15]. In addition, strabismus is common in patients with thyroid disorders as a result of the impairment of the extraocular muscles, which results in head tilt and diplopia. Diplopia usually occurs in patients with thyroid disorders due to the inflammation and swelling of the extraocular muscles[14]. Therefore, due to the changes in tear evaporation rate, tear osmolarity and altered eyelid structure, dry eye syndrome is usually seen in patients with thyroid disorders[16]. The onset of the various different signs and symptoms of patients with thyroid disorders differs amongst patients. They can be seen simultaneously or take up to several months or years to manifest themselves.

Evidence has emerged to suggest that the ocular inflammation mediated by T lymphocytes plays a critical role in the pathogenesis of dry eye syndrome by reducing the production of aqueous tears[15]. The damage sustained by the ocular surface in patients with thyroid disorders is associated with a reduction in tear production due to the involvement of the lacrimal gland[17].

Our study revealed development of dry eye in post throidectomy patients (38. 5%). After extensive literature search, we did not find similar studies done in post thyroidectomy patients. A more detailed study is needed in order to better understand the situation and the factors which cause such phenomenon after surgery.

CONCLUSION

In conclusion, ophthalmopathy may develop in patients after thyroid surgeries for thyroid diseases. Interstingly, dry eye was more common occurrence in these patients compared to TAO. The mechanism by which such eye dryness occurs is not yet clear, although several factors have been cited including low tear production, excessive tear evaporation, tear instability, and disturbances in the tear film lipid layer. A more detailed study is needed in order to better understand the situation and which factors cause such phenomena to occur. Thyroid hormonal function and TSH receptor antibody tests, yielded abnormal results in most patients that showed ophthalmic symptoms. Our results, combined with previous literature, indicated several possibilities for the pathogenesis of TAO. First, euthyroid TAO may be caused by thyroid tissues that remain after total thyroidectomy. secondly, the surgery itself may lead to ophthalmopathy. We recommend that all post throidectomy patients should undergo eye examination for TAO in follow up period

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