

Thyroid Associated Orbitopathy Following Periocular Surgery

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Purpose: To describe a series of patients in which Thyroid Associated Orbitopathy (TAO) occurred after periocular surgery.

Methods: A retrospective case review of patients who developed TAO in close temporal association with periocular surgical interventions and presented at the orbital clinic from 1997 to 2004. History of previous thyroid abnormality and the lack of TAO signs and symptoms before surgery were reviewed and analyzed.

Results: Nine patients that developed TAO in association with periocular surgery were identified. All were women with an average age of 59.3 years. (range: 45-75 years). The patients divided into two groups. Group 1 consisted of four patients who had previously been diagnosed with Graves' hyperthyroidism (GH). They ranged in age from 48 to 75 years (average: 58.8 years). The diagnosis of GH had been made an average of 50.5 months (range: 12-96 months) before presentation with TAO. Group 2 consisted of five patients who had no previous history of thyroid abnormality. They ranged in age from 45 to 74 years (average: 60.2 years). No patients had any signs or symptoms of TAO before their recent presentation.

Conclusions: Periocular surgery may lead to local inflammatory events that may contribute to the instigation of TAO in predisposed individuals. *Korean Journal of Ophthalmology* 20(2):82-86, 2006

Key Words: Periocular surgery, Thyroid associated orbitopathy

Thyroid associated orbitopathy (TAO) was described by Graves in 1835¹ and by Von Basedow in 1840.² TAO occurs in 25 to 75% of immune mediated dysthyroidism patients with variable severity.³

TAO is associated with a hyperthyroid state in 85% of cases.³ In a smaller percentage of cases the orbitopathy may be associated with Hashimoto's thyroiditis (5%) or a euthyroid state (10%).^{3,4,5,6,7} TAO can predate a dysthyroid state in up to 20% of cases.³ The immune dysregulation produces both orbitopathy as well as the dysthyroid state, although the temporal relationship between the two varies. The etiology of TAO is unknown but causative factors include genetic predisposition, infections with viruses and Yersinia, stress, and smoking when preceded by Graves' hyperthyroidism. The view that TAO is an autoimmune process is suggested by the coexistence with other auto-

immune diseases such as Myasthenia Graves disease, systemic lupus erythematosus, and vitiligo.^{4,5,6,7,8}

We present a series of nine patients in whom periocular surgery is possibly related to the initial presentation of TAO.

Materials and Methods

A retrospective case review was performed to identify patients who developed TAO in temporal association with periocular surgery. Patients who presented from 1997 to 2004 were analyzed.

The diagnosis of TAO was made using clinical signs and symptoms. Patients were examined for proptosis, lid retraction and lid lag, extraocular motility abnormalities, and periocular swelling. A standard assessment including slit lamp examination and color vision testing was also performed. Radiological investigations (MRI or CT) were used to confirm clinical impressions and define extraocular muscle and orbital fat involvement.

University Institutional Review Board (IRB) / Ethics Committee approval was obtained by authors.

Results

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Nine patients were identified, all of which female, ranging in age from 45-75 years (average: 59.3 years). This represents an incidence of 1.6% in our clinic population.

Nine patients were identified comprising two main groups. Group 1 was comprised of four patients who had previously been diagnosed with Graves' hyperthyroidism. They ranged in age from 48-75 years (average: 58.8 yrs). The diagnosis of Graves' hyperthyroidism had been made 12 to 96 months (average: 50.5 months) prior to presenting with orbitopathy.

Group 2 was comprised of five patients who were not documented to have had any previous or concurrent thyroid abnormality. They ranged in age from 45-74 years (average: 60.2 years).

None of the patients had previously been diagnosed with TAO in relation to their Graves' disease

The periocular procedures performed are summarized in Table 1.

1. Group 1: Patients with Previous Diagnosis of Thyroid Abnormality

Four patients had been diagnosed as having Graves' hyperthyroidism before surgery. All of these patients had been stable with no signs of TAO for an average of over four years before periocular surgery.

Here we present two interesting cases in group 1.

Patient 1

This 48-year-old patient developed Graves' disease in June of 1994 at age 38. She was treated with Iodine 131 and rendered euthyroid upon replacement thyroxine treatment.

In November 1999 she underwent bilateral LASIK surgery to correct her myopia. Immediately after surgery she noted swelling in the left eye. In December 1999 it was noted that she had proptosis in both eyes and left upper lid retraction. A CT scan showed an enlargement of both inferior rectus muscles. TSH and T3 levels were slightly elevated but she was essentially euthyroid. She was observed until she was stable and, in June of 2003, underwent a bilateral fat decompression for cosmesis, followed by left upper lid retraction repair.

Patient 2

This 59-year-old patient was diagnosed with Grave's

hyperthyroidism at 24 years of age and was treated for 12 months with methimazole, by which time her thyroid levels had normalized. She required no further treatment until September 2001 when, at the age of 56, she again developed Graves hyperthyroidism. After an initial six-months treatment period with methimazole, she was treated with Iodine 131 in April of 2002. Iodine 131 was subsequently replaced with thyroxine and the patient was considered euthyroid.

In September of 2002 she underwent Botox injections to her eyelids and brow. It was noted that she had marked swelling after the injections and, in the next one to two months, developed bilateral lid retraction. There was no sign of proptosis or diplopia. At the time of presentation, the TSH level was normal, T4 was slightly elevated, and anti- thyroid peroxidase antibody was positive.

She did not develop any further signs of TAO and in February of 2004 underwent bilateral lid retraction repair with good postoperative results.

2. Group 2: Patients with No Previous Thyroid Abnormality

Five patients did not have any history of dysthyroid state or TAO before their periocular surgery.

Two interesting cases in group 2 are presented here.

Patient 1

This 74-year-old patient underwent left cataract extraction with retrobulbar injection in October of 1999. Postoperatively, she noted swelling and two months later developed left upper lid retraction. She noted pain and burning in her eyes and developed vertical diplopia. Thyroid function tests showed normal T4 and T3 levels and a mild suppression of TSH with positive TSH receptor antibodies.

In April of 2000 she was noted to have mild bilateral proptosis that was more severe in the left eye, and left upper lid retraction. An MRI showed an enlarged left superior rectus muscle. Because of the atypical presentation she underwent biopsy of the enlarged muscle in October 2000, which showed inflammatory changes consistent with Graves' hyperthyroidism. The diplopia slowly worsened and in June 2001 a CT scan showed bilateral enlargement of all extraocular muscles, which was greater in the left eye. After spontaneous stabilization of the orbitopathy she underwent bilateral strabismus surgery in July 2001 and again in July 2002 to treat her diplopia.

She remained euthyroid until October 2003 when she developed clinical hyperthyroidism with grossly elevated T4 and suppressed TSH. She began methimazole treatment for her Graves' hyperthyroidism in December 2003.

Patient 2

This 71-year-old patient underwent cosmetic surgery consisting of facelift, bilateral upper lid blepharoplasty, and lower lid laser resurfacing in December 2002. She noted

Table 1. Types of periocular surgery

Type of surgery	(Group I) Previous Hyperthyroidism without TAO	(Group II) No History of thyroid Disease
Botox injections	1	
Cataract surgery	1	1
Injectable fillers		1
LASIK	1	
Facelift / blepharoplasty / laser resurfacing / forehead lift	1	3

significant postoperative edema that was worse on the left side, and in January 2003 prominence of her left eye. Upon examination she was noted to have left eye proptosis, brow swelling, and limited elevation of the left globe. An MRI showed enlargement of the left inferior rectus, as well as mild enlargement of the left superior and lateral rectus.

In March 2003 she developed hyperthyroidism with elevated T4 and suppressed TSH, and began PTU therapy. In May 2003 she developed left compressive optic neuropathy and was treated with prednisone and orbital radiotherapy. The prednisone treatment was tapered to zero and by December 2003 her vision had stabilized.

We present a series of four patients among nine who developed TAO in temporal relationship to periocular surgery. There were five patients (Group 2) without a history of thyroid dysfunction prior to surgery. Four of these patients subsequently developed Graves' hyperthyroidism (This occurred 2, 3, 11, and 48 months after TAO diagnosis) and the fifth tested positive for auto-antibodies.

In each of these patients there was a temporal relationship between their surgery and the development of TAO. In all patients TAO developed within six weeks of the periocular surgery.

All patients developed proptosis and upper lid retraction and four of the five had diplopia due to extraocular muscle enlargement. Two patients developed compressive optic neuropathy that required steroid and orbital radiotherapy. Two patients underwent orbital decompression for cosmesis after stabilization of the TAO. Four of the five patients required lid surgery, and three of five required extraocular

muscle surgery.

Four patients had previous history of thyroid abnormality (Group 1). In all patients there was significant lid retraction, three of four developed diplopia, and one patient developed compressive optic neuropathy.

A summary of the cases is presented in Table 2.

Discussion

We studied nine patients in whom surgery on or around the eye was temporally associated with the development of TAO, both in patients with previously stable Graves' hyperthyroidism and in patients with no previous thyroid disease history. Before discussing this group of patients further it is important to note how they differ from previously described TAO patients. All patients were euthyroid at the time of TAO, which is uncommon with most patients developing TAO in the setting of systemic hyperthyroidism or more uncommonly, hypothyroidism.^{3,9,10}

Five patients (Group 2) had no previous thyroid abnormality. Four patients (Group 1) had been treated for Graves' hyperthyroidism. While it may be argued that the development of TAO was part of the natural history of the disease, three of the four patients had stable Graves disease for at least 29 months before the surgical event. Bartley reported that the usual temporal relationship of hyperthyroidism and the development of TAO is 18 months in 85% of patients.^{3,9,10} Our observed time interval falls outside that expected between thyroid dysfunction and the development of orbitopathy. In only 15% of cases does TAO develop

Table 2. Summary of patient characteristics

Patient	Age	Previous Hyperthyroidism	Type of Surgery	Signs of TAO	Time of surgery to orbitopathy (weeks)	Sex	Time Graves to Surgery (months)	Thyroid abnormality
1	59	Yes	Botox injection to eyelids and brow	LR LS	4	F	12	Euthyroid
2	53	Yes	4 lid blepharoplasty	LR/LS/REM/P/D	4	F	96	Euthyroid
3	75	Yes	Cataract/RBA	LR/REM/P/D/ONC	4	F	29	Euthyroid
4	48	Yes	LASIK	LR/LS/P	4	F	65	Euthyroid
5	74	No	Cataract/RBA	LR/LS/D/P	6	F	N/A	Developed Graves'
6	71	No	Facelift/4 lid blepharoplasty/ Laser resurfacing	P/REM/ONC	4	F	N/A	Developed Graves'
7	61	No	Facelift/4 lid blepharoplasty/ chin implant	LR/REM/ ONC/D	4	F	N/A	Developed Graves'
8	48	No	Bilateral UL blepharoplasty	REM/D/P	8	F	N/A	Developed Graves'
9	45	No	Hyaluronic acid injection	LR/LS/D/P	4	F	N/A	Euthyroid Increased Thyroid autoantibody

KEY: LR-lid retraction; RBA-retrobulbar anesthetic; LS-lid swelling; REM-restricted eye movement; P-proptosis; D-diplopia; ONC-optic nerve compression

before or after this time period. One of the four patients had Botox injections 12 months after the diagnosis of Graves' disease, and it could be argued that the development of TAO was merely coincidental to the treatment. Two patients with previous Graves' hyperthyroidism developed TAO at least five years after their original diagnosis.

It is of note that all patients were women. The usual ratio of women to men when one considers TAO is around six to one.⁹ The average age of the patients in this study was 59.3 years, which corresponds to the second peak in the bimodal distribution of TAO seen in women.^{9,11}

The pathogenesis of TAO has been a topic of controversy for many years. The instigation of the extrathyroidal manifestations of Graves' disease and other dysthyroid states has yet to be explained. The original description by Graves and Von Basedow in the 1830s¹² included pretibial myxedema, hyperthyroidism, and Orbitopathy, and for years a common auto-antigen has been sought.¹² Initially extraocular muscle antigens 13 and the TSH receptor were considered likely auto-antigens.¹⁴ These antigens are however not limited to the sites that manifest changes in Graves disease.¹⁵

More recently the central role of the unique orbital fibroblast has been implicated in TAO.^{16,17} Studies have identified the role of the orbital fibroblast as a target of the T-cell mediated infiltration of the orbital connective tissues. Orbital and pretibial fibroblasts possess unique phenotypic behavior. Orbital fibroblasts in particular are neural crest derived¹⁷ and express CD40 (a typical B-cell cell surface receptor) that can be activated by T-cell receptor (CD154) linkage to elicit inflammatory cytokines and bone marrow derived cell migration factors.^{18,19}

Moreover, a subpopulation of orbital fibroblasts can undergo adipocyte differentiation *in vitro* when placed in appropriate culture media, and can be induced by 20 inflammatory cytokines to produce up to a 100-fold greater amount of glycosaminoglycan than normal fibroblasts.^{21,22} These latter two properties explain the exaggerated, glycosaminoglycan deposition and fat proliferation observed in TAO patients.²³ The effect on the orbits can be unilateral in as many as 10% of cases.

It is difficult to find any previous analysis of the type of patients examined in this study.

Some authors have suggested that trauma and pressure may play a central role in the sites of extrathyroidal manifestations of TAO.^{24,25} Previous authors have described TAO as a cause of diplopia after cataract surgery.²⁶ These authors described 58 patients who developed unexpected diplopia after cataract surgery. It was found that eight of these patients had concurrent TAO. Three patients had been previously diagnosed with stable Graves' hyperthyroidism, two subsequently developed dysthyroid changes, and three patients were euthyroid. In seven patients, retrobulbar anesthetic injection was used for the cataract surgery.

Previously, authors have postulated traumatic aggravation of subclinical TAO as the explanation for the symptoms. A

single case report of TAO in a previously stable Graves' hyperthyroidism patient²⁷ postulates a local pressure mechanism for the induction of TAO, and extrapolates this to suggest that local factors are the main determinant of the extrathyroidal manifestations of dysthyroid states. In this particular case, the patient had previously stable hyperthyroidism and developed TAO after cataract extraction with retrobulbar anesthesia. It has also been suggested that Iodine 131 treatment can exacerbate or incite TAO in the acute phase of Graves' hyperthyroidism.²⁸

The role of localized trauma from periocular surgery may be central to TAO development in the nine patients identified in this study.

It may be that, in the patients with a pre-existing dysthyroid state, the local trauma of the surgery led to inflammation in a pre-sensitized host that stimulated the development of TAO. In the subset of patients with no previous dysthyroid state (Group 2), other factors may also be involved. Surgery may lead to the development of TAO and Graves' hyperthyroidism in predisposed patients. These immunologically susceptible people may be impacted by local mechanisms that prime site-specific responses.

It is of note that smoking imposes a seven-fold increased risk for the development of TAO in people who develop thyroid dysfunction. The mechanism for this is unknown, but it may be related to microvascular ischemia that causes anoxic responses in all tissues, but the site specificity is granted via particular cell types in the orbit. Local trauma may lead to local inflammatory pathways sensitizing orbit-specific cells and priming the immune system to various site-specific antigens including the orbit and thyroid gland.

It is possible that the five patients (Group 2) who had no history of dysthyroid state may have had subclinical Graves' hyperthyroidism in which the progression to TAO was simply coincidental with the surgery they underwent. However, no constant symptom during the detailed history review was found to suggest this.

It is important to quickly identify this subgroup of patients as the manifestations of TAO are more severe in middle aged or older patients,³ and certainly three patients in this study required systemic treatment, radiotherapy, and eventual surgery to alleviate compressive neuropathy due to their TAO.

Although it is difficult to generalize a condition with such protean manifestations, it may be reasonable to screen patients on a history basis for any immunological mediated thyroid disease.

We do not necessarily advocate thyroid function tests for all preoperative patients, but in many centers they are routinely done as part of the preoperative workup. There may be a role for preoperative baseline blood work to detect the use of systemic steroids before periocular surgery in a patient that gives a history of a previous immunological mediated dysthyroid state.

Shortcomings of this study are the lack of a control group

and the small number of participants.

Additional case-control studies will be needed to identify the cause-and-effect relationship between TAO and periocular surgery.

Conclusion

In this paper we present nine patients who developed TAO of varying severity after cataract surgery or cosmetic surgery around the orbit. This may be related to the local inflammatory process stimulating exaggerated autoimmune responses in predisposed individuals. Furthermore, it may be important to counsel patients with pre-existing dysthyroid states undergoing surgery about the possibility of exacerbating their condition.

Lastly, in cosmetic surgery patients, any prolonged recovery or development of diplopia or lid retraction may prompt an investigation for TAO.

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