Scholars Journal of Applied Medical Sciences (SJAMS)
Abbreviated Key Title: Sch. J. App. Med. Sci.
©Scholars Academic and Scientific Publisher
A Unit of Scholars Academic and Scientific Society, India
www.saspublishers.com

ISSN 2320-6691 (Online)
ISSN 2347-954X (Print)

Ophthalmology

Thyroid Associated Ophthalmopathy: Prevalence, Association & Risk Factors

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Original Research Article

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Article History
Received: 13.06.2018
Accepted: 21.06.2018
Published: 30.06.2018

DOI:
10.36347/sjams.2018.v06i06.036

Abstract: Thyroid-associated ophthalmopathy (TAO) is an autoimmune disease of the retroocular tissues occurring in patients with Graves' disease. The aim of the present study was to determine the prevalence of TAO among Indian patients with thyroid dysfunction and the risk factors associated with TAO. This was a retrospective, hospital based and non-interventional study conducted at Department of Ophthalmology and General Medicine of two tertiary care centres. The duration of study was 6 months; January-2018 to June-2018. 50 adult patients (age >18 years) of thyroid disorder with orbitopathy were evaluated for possible inclusion in this study. An ophthalmologist interviewed the patients and noted the presence of symptoms and signs relevant to thyroid eye disease. Total 50 patients were eligible for study. Out of a total of 50 patients who were eligible for analysis, 38 were diagnosed with mild to moderate TAO and 12 were diagnosed with severe TAO. There were older patients among those with severe courses than in the group with mild to moderate courses (*t*-test, $p = 0.007$). There were more male patients in patients with a severe course (83.33%) compared to those with a mild to moderate course (63.15%), this difference was statistically significant. More patients with a severe course were smokers compared to those with a mild to moderate course. More patients with a severe course had a higher clinical activity score ($p = 0.006$). Our study confirmed that smoking is the strongest risk factor for development of a severe course of TAO in Indian patients. Thus, it is important for patients with Graves' disease to refrain from smoking.

Keywords: TAO, grave's disease, autoimmune.

INTRODUCTION

Thyroid-associated ophthalmopathy (TAO) is an autoimmune disease of the retroocular tissues occurring in patients with Graves' disease. Although it has often been referred to as Graves' ophthalmopathy, it is primarily a disease of the orbit and is better termed Graves' orbitopathy[1-3]. In Graves' disease, the main autoantigen is the thyroid-stimulating hormone (TSH) receptor (TSHR), which is expressed primarily in the thyroid but also in adipocytes, fibroblasts, and a variety of additional sites. TSHR antibody and activated T cells also play an important role in the pathogenesis of Graves' orbitopathy by activating retroocular fibroblast and adipocyte TSHR [4]. The volume of both the extraocular muscles and retroocular connective tissue is increased, due to fibroblast proliferation, inflammation, and the accumulation of hydrophilic glycosaminoglycans (GAG), mostly hyaluronic acid [5,6]. GAG secretion by fibroblasts is increased by thyroid-stimulating antibodies and activated T cells (via cytokine secretion), implying that both B and T cell activation are integral to this process. The accumulation of hydrophilic GAG in turn leads to fluid accumulation, muscle swelling, and an increase in pressure within the orbit. These changes, together with retroocular adipogenesis, displace the eyeball forward, leading to extraocular muscle dysfunction and impaired venous drainage. Approximately 20 to 25 percent of patients with Graves' hyperthyroidism have clinically obvious Graves' orbitopathy [7]. Most patients have mild disease, whereas approximately 5 percent have moderate to severe disease. The evidence for a genetic component to the pathogenesis of Graves' hyperthyroidism applies equally to the associated orbitopathy. A family history of Graves' disease or Hashimoto's disease, the presence of other autoimmune diseases in the patients and their relatives, and a high percentage of concordance in identical twins (depending on their age), all point toward a major genetic component in these disorders [8]. There is, however, no confirmed, reproducible evidence of a distinct genetic risk for eye disease itself. The aim of the present study was to determine the prevalence of

TAO among Indian patients with thyroid dysfunction and the risk factors associated with TAO.

MATERIALS AND METHODS

Study Design: This was a retrospective, hospital based and non-interventional study.

Study Setup: This study is conducted at Department of Ophthalmology and General Medicine of two tertiary care centres.

Study Duration: The duration of study was 6 months; January-2018 to June-2018.

Sampling: Purposive sampling technique is used for selection of desired samples according to inclusion criterion.

Sample Size: 50 adult patients (age >18 years) of thyroid disorder with orbitopathy were evaluated for possible inclusion in this study.

Inclusion criteria: Thyroid disorder with orbitopathy

Exclusion criteria: Patients with thyroid gland malignancy and thyroid nodules were excluded from the study.

Methods: Demographic data, past medical history, family history, and life-style data were collected from all patients. An ophthalmologist interviewed the patients and noted the presence of symptoms relevant to thyroid eye disease using the VISA classification including vision, inflammatory, strabismus, and appearance categories.[9] For the patients with eye symptoms, the ophthalmologist performed an ophthalmic examination. Patients with at least one symptom and one sign in any category in the VISA classification were considered to have thyroid eye disease.

The diagnosis of TAO was based on the presence of typical clinical features of the disease, including eyelid retraction, proptosis, impaired motility, and increase in intraocular pressure on upward gaze, one or more enlarged extraocular muscles, and increased infraorbital fat on computed tomography scans. In this study, a mild course of TAO was defined as proptosis less than 21 mm with no or only intermittent diplopia without optic nerve involvement. Moderate TAO was defined as proptosis between 21 mm and 23 mm with intermittent diplopia and no optic nerve involvement [10]. Patients were judged to have a severe course of TAO if they had, in the worse eye, either motility impairment causing constant diplopia within 30 degrees by the binocular single visual field test and the Hess screen; or proptosis greater than 23 mm or with a difference between eyes of more than 5 mm by Hertel exophthalmometry, causing serious exposure keratopathy; or compressive optic neuropathy.

Statistical Technique: Microsoft Excel® and SPSS® 20 for Windows® were used for data storage and analysis. The qualitative data were expressed in percentages and quantitative data were expressed as mean ± standard deviation. Student's t test and Chi-Square test were used to determine statistical difference between variables.

RESULTS

Total 50 patients were eligible for study. Out of a total of 50 patients who were eligible for analysis, 38 were diagnosed with mild to moderate TAO and 12 were diagnosed with severe TAO. Demographic, clinical, and biochemical features of mild to moderate TAO and severe TAO are compared in Table 1. There were older patients among those with severe courses than in the group with mild to moderate courses (*t*-test, $p = 0.007$). There were more male patients in patients with a severe course (83.33%) compared to those with a mild to moderate course (63.15%), this difference was statistically significant. The initial free T4 levels were high (above 3 ng/dL) in 73.68% of the mild to moderate group and 66.66 of severe group cases. All patients of both groups had positive TBII. Comorbid illnesses like diabetes and hypertension were almost similar in both groups. More patients with a severe course were smokers compared to those with a mild to moderate course. More patients with a severe course had a higher clinical activity score ($p = 0.006$).

On multiple logistic regression analysis, smoking behaviour was found to be a risk factor for severe TAO with an odds ratio of 0.326.

DISCUSSION

Graves' orbitopathy, an autoimmune disease of the retroocular tissues, occurs in 20 to 25 percent of patients with Graves' disease. The main autoantigen is the thyroid-stimulating hormone (TSH) receptor (TSHR), which is expressed primarily in the thyroid but also in adipocytes, fibroblasts, and a variety of additional sites. TSHR antibody and activated T cells play an important role in pathogenesis of Graves' orbitopathy by activating retroocular fibroblasts and adipocytes. The volume of both the extraocular muscles and retroocular connective and adipose tissue is increased, due to inflammation and the accumulation of hydrophilic glycosaminoglycans (GAG), principally hyaluronic acid, in these tissues. GAG secretion by fibroblasts is increased by activated T cell cytokines and by the activation of the receptors for TSH and insulin-like growth factor-1 (IGF-1).

Table-1: Comparison of demographic, clinical, and biochemical features between patients with mild to moderate courses and severe courses of thyroid-associated orbitopathy

Characteristics	Mild to Moderate Course (n=38)	Severe Course (n=12)	p Value
Age (yrs)	36 ± 5.8	54 ± 4.4	0.007
Male	24 (63.15%)	10 (83.33%)	0.006
Initial fT4 level (> 3 ng/dl)	28 (73.68%)	8 (66.66%)	NS
Positive TBII	38 (100%)	12 (100%)	NS
Comorbidities Diabetes Hypertension	 5 (13.15%) 14 (36.84%)	 1 (8.33%) 4 (33.33%)	 NS NS
History of Smoking	11 (28.94%)	11 (91.66%)	0.005
Exophthalmos	18.5 ± 2.4	19.6 ± 3.6	0.025
Lid Retraction	19 (50%)	7 (58.33%)	NS
Clinical Activity Score	1.2 ± 1.2	2.7 ± 2.3	0.006

NS= nonsignificant

Risk factors for the development of Graves' orbitopathy include genetics, male sex, smoking, and prior radioiodine therapy. The major ocular symptoms include one or more of the following: a sense of irritation in the eyes; excessive tearing that is often made worse by exposure to cold air, wind, or bright lights; eye or retroocular discomfort or pain; blurring of vision; diplopia; and occasionally, loss of vision. The characteristic signs of Graves' orbitopathy are proptosis and periorbital edema. In the majority of patients, orbitopathy occurs in the setting of current or past Graves' hyperthyroidism (low TSH, high free thyroxine [T4] and/or triiodothyronine [T3]), but in approximately 10 percent of patients, Graves' thyroid disease is absent. Orbitopathy appears before the onset of hyperthyroidism in approximately 20 percent of patients, concurrently in approximately 40 percent, in the six months after diagnosis in approximately 20 percent, and after treatment for Graves' hyperthyroidism in the remainder (most commonly after radioiodine therapy). In most patients, the diagnosis of Graves' orbitopathy is obvious because of the combination of the characteristic ocular abnormalities (proptosis, periorbital edema) and hyperthyroidism. In moderate to severe disease, noncontrast computed tomography scanning may give an assessment of the risk of future optic nerve compression by enlarged extraocular muscle at the orbital apex and is sometimes helpful in the differential diagnosis. Activity of disease, assessed using the clinical activity score, is useful for determining therapy and gauging response to that therapy. Severity of disease is an independent measure that assesses threat to vision and the degree of proptosis and soft tissue involvement.

CONCLUSION

Our study confirmed that smoking is the strongest risk factor for development of a severe course of TAO in Indian patients. Thus, it is important for patients with Graves' disease to refrain from smoking.

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