

A NON-RANDOMISED PROSPECTIVE STUDY OF THYROID ORBITOPATHY IN A TERTIARY CARE CENTRE

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ABSTRACT

Graves' disease is an autoimmune condition where TSH receptors are targeted by the auto-antibodies. Although most patients have clinical or laboratory evidence, the disease process can occur even in the absence of detectable thyroid abnormality. Although most cases of TAO can be managed medically without any visual loss, it may result in exposure keratitis and compressive optic neuropathy. There was female preponderance noted. Maximum number of patients were in the 25-50 years of age group. More than 65% of the patients were hyperthyroid followed by euthyroid in 25% and then hypothyroid in less than ten percent. In both the sexes, the hyperthyroid status was the most common followed by euthyroid and hypothyroid. No male was reported to be hypothyroid. The most common presentation was found to be bilateral than unilateral. Inferior rectus was the commonest muscle involved followed by medial rectus, superior rectus-LPS complex and lateral rectus in descending order. Incidence and various modes of presentation of 'Thyroid Orbitopathy' of our study at our tertiary centre in Hyderabad are correlating with national and international studies.

KEYWORDS

Thyroid, Graves, Orbitopathy, TED, TAO, GO.

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INTRODUCTION: Graves' disease is an autoimmune condition where TSH receptors are targeted by the autoantibodies. 40% of patients develop orbital manifestations known as Graves' Orbitopathy (GO) or Thyroid-associated orbitopathy (TAO). Although most patients have clinical or laboratory evidence, the disease process can occur even in the absence of detectable thyroid abnormality. Euthyroid or Ophthalmic Graves -wherein the eye signs of Graves' disease occur in patients who are not clinically hyperthyroid. Thyroid orbitopathy usually occurs within 18 months of hyperthyroidism.

Although most cases of TAO can be managed medically without any visual loss, it may result in exposure keratitis and compressive optic neuropathy. Current therapeutic options for reducing the inflammation during active disease are corticosteroids, external radiation and steroid-sparing immunosuppressive agents, and for inactive disease is surgery for correcting the residual abnormalities secondary to fibrosis.

REVIEW LITERATURE: Bartley GB, et al. conducted an incidence cohort study on "Clinical features of Graves' ophthalmopathy" and the study concluded that eyelid retraction was the most common clinical sign of Graves' ophthalmopathy. The common constellation of typical features (hyperthyroidism, eyelid retraction, exophthalmos, restrictive extraocular myopathy, and optic nerve dysfunction) occurred relatively infrequent.¹

Gerding MN, et al. conducted a study on "Association of thyrotropin receptor antibodies with the clinical features of Graves' ophthalmopathy" and the study concluded that TSH-R antibody levels correlate directly with clinical features of Graves' ophthalmopathy. The results support the hypothesis of a pathogenic role of TSH-R antibodies and TSH-R in the orbit of Graves' ophthalmopathy patients.²

Yamada M, et al. conducted a study on "Thyroid-associated ophthalmopathy: Clinical features, pathogenesis, and management." And the study concluded that antibodies against type XIII collagen, which is localised in the plasma membranes of orbital fibroblast, may be a new marker for the congestive ophthalmopathy subtype of Thyroid-associated ophthalmopathy. The measurement of antibodies against key eye muscle and orbital connective tissue autoantigens could have a role in the management of active ophthalmopathy and its prediction in patients with Graves' hyperthyroidism.³

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Orgiazzi J, Madec AM. conducted a study on "Reduction of the risk of relapse after withdrawal of medical therapy for Graves' disease." and the study concluded that the reduction of the risk of relapse in patients with medically treated hyperthyroid Graves' disease relies on clinical competence and appropriate management taking into account an array of factors none of which alone has definite predictive value.⁴ Karasek M, et al. conducted a study on "Aetiopathogenesis of Graves' disease" and the study concluded that Graves' disease is an autoimmune disorder, caused by thyroid-stimulating antibodies, which bind to and activate the thyrotropin receptor on thyroid cells, inducing the synthesis and release of thyroid hormones. It is a polygenic and multifactorial disease that developed as a result of complex interaction between genetic susceptibility and environmental and/or endogenous factors. Graves' disease differed from other autoimmune diseases of thyroid by specific clinical features, including hyperthyroidism, vascular goitre, ophthalmopathy and less common infiltrative dermopathy.⁵ Bartalena L, et al. conducted a study on "Relationship between management of hyperthyroidism and course of the ophthalmopathy" and the study concluded that in patients with severe Graves' Orbitopathy, treatment of hyperthyroidism and management of Graves' Orbitopathy proceed independently of each other, and either definitive (radioiodine or thyroidectomy) or conservative (antithyroid drugs) treatment for hyperthyroidism could be selected while treating Graves' Orbitopathy. The author preferred to the former, because it depleted intrathyroidal autoreactive T-lymphocytes and removed thyroid antigens, which were likely to be involved in the pathogenesis of autoimmune reactions of the orbitopathy.⁶

Fernandez Hermida RV, et al. conducted a study on "Clinical manifestations of thyroid ophthalmopathy." and the author recommends the use of objective measurements for proptosis, extraocular movements, corneal alterations, and the optic nerve, using the clinical activity scale or a recorded change in objective measurements to document disease activity, and lastly, documenting the patients' perception of their disease status.⁷

Vladutu C, et al. conducted a study on "Therapeutic options in thyroid ophthalmopathy" and the study concluded that the conservative treatment of the thyroid myopathy is efficient only in the acute phase. And the author concluded that the surgical treatment should be applied when muscular fibrosis and restrictive strabismus were present. The timing of surgery was indicated after 6 months of stable ocular deviation. Adjustable surgery was the most suitable procedure for the restrictive strabismus in thyroid myopathy.⁸

Lim SL, et al. conducted a study on "Prevalence, risk factors, and clinical features of thyroid-associated ophthalmopathy in multiethnic Malaysian patients with Graves' disease", and the study concluded that the thyroid-associated ophthalmopathy has relatively high prevalence rate (34.7%) in three populations of Asian patients with Graves' disease. This was similar to that reported for Caucasian patients with Graves' disease. As in Caucasian

patients, smoking increased the risk of thyroid-associated ophthalmopathy. In the Asian populations, exophthalmos was the most common eye sign. However, lower lid retraction was common and present in 60% of cases with other signs of thyroid-associated ophthalmopathy. In Chinese, Malay and Indian Asians with Graves' disease, lower lid retraction should be a diagnostic criterion for thyroid-associated ophthalmopathy.⁹

Chan LL, et al. conducted a study on the "Graves' Ophthalmopathy: The bony orbit in optic neuropathy, its apical angular capacity, and impact on prediction of risk." And the study concluded that bony orbital angles, length of the lateral orbital wall, muscular diameters, muscular bulk of the medial rectus muscle relative to the bony orbit, and apical crowding were associated with clinical optic neuropathy. And orbital wall angles, especially the medial wall, and muscular enlargement are independent risk predictors.¹⁰

Konuk O, et al. conducted a study on "Intraocular pressure and superior ophthalmic vein blood flow velocity in Graves' Orbitopathy: Relation with the clinical features." And the study concluded that intraocular pressure and superior ophthalmic vein blood flow velocity have significant association with the clinical features of Graves' Orbitopathy. The decrease in superior ophthalmic vein blood flow velocity increases the severity of Graves' Orbitopathy, and may have a role in the clinical course of dysthyroid optic neuropathy.¹¹ Douglas RS, et al. conducted a study on "The pathophysiology of thyroid eye disease: implications for immunotherapy". The author said progressive advances in the understanding of the immunopathogenesis of Thyroid Eye Disease continue to spur clinical trials utilising targeted immune therapies. Continued understanding of the molecular mechanisms of disease will expand potential treatments for Thyroid Eye Disease patients and obviate the need for reconstructive surgical therapies.¹²

Ponto KA, et al. conducted a study on "Clinical relevance of thyroid-stimulating immunoglobulins in Graves' ophthalmopathy" and the study concluded that the thyroid-stimulating immunoglobulins show more significant association with clinical features of Graves' orbitopathy than TBII (thyrotropin receptor binding inhibitory immunoglobulin assay) and may be regarded as functional biomarkers for Graves' Orbitopathy.¹³

Alves M, et al. conducted a study on "Thyroid-associated orbitopathy". Thyroid-associated orbitopathy is a clinical entity with pathogenic mechanisms not fully understood, and appears in about 90% of cases in association with hyperthyroidism of Graves' disease. Its approach involves the recognition of typical features and the exclusion of other disease in the less common presentations. The treatment is conditioned by the determination of the activity and severity of the disease. The restoration of the euthyroid state and avoiding of hypothyroidism are essential in mitigating the progression of orbitopathy. Glucocorticoid intravenous therapy is the treatment of choice in the active phase and surgical treatment in the inactive phase. Radiotherapy and cyclosporine in combination with

corticosteroids are alternatives when monotherapy is insufficient in the active phase. Treatment should be instituted in specialised centres, with ophthalmologists and endocrinologists acting in synergy to avoid consequences of delays in intervention and in optimising therapy.¹⁴

Dolman PJ. conducted a study on "Evaluating Graves's orbitopathy." The author concluded that diagnosis of GO is based on recognition of clinical features and may be supported by thyroid function and immune testing, and orbital imaging. The endocrinologist or internist may play an important role in early recognition and diagnosis of GO, in grading severity and activity, and in arranging appropriate referral to an ophthalmologist based on this evaluation.¹⁵

Chng CL, et al. conducted a study on "Ethnic differences in the clinical presentation of Graves' ophthalmopathy." and the study said there is some evidence to suggest Asian patients with GO may manifest milder phenotypic features of GO, with less proptosis and evidence of extraocular muscle involvement and restriction. The reason for these differences were likely to be multifactorial and include orbital and lid anatomy, genetic background and autoimmune responses including TSH- receptor antibodies.¹⁶

Reddy SV, et al conducted a study on "Prevalence of Graves's ophthalmopathy in patients with Graves' disease presenting to a referral center in north India." And the study concluded that the prevalence of Graves's ophthalmopathy (GO) varied widely in different ethnic groups. Indians have been reported to have a lower prevalence of Graves's ophthalmopathy as compared to Caucasians of European origin. From the study, author concluded that among north Indian patients with GO studied at a referral center, the prevalence of GO was similar to Caucasians of European descent, but clinically active and severe ophthalmopathy was uncommon.¹⁷

Menconi F, et al. conducted a study on "Spontaneous improvement of untreated mild Graves's ophthalmopathy: Rundle's curve revisited" and the study concluded that in confirmation of Rundle's observation, untreated GO improved spontaneously with time in the majority of patients, with an activity peak between 13 and 24 months, which may have implications in determining the proper timing of GO treatments.¹⁸

Pawlowski P, et al. conducted a study on "Elevated percentage of HLA-DR and ICAM-1 conjunctival epithelial cells in active Graves's orbitopathy". The author concluded that the percentage of HLA-DR and ICAM-1 conjunctival

epithelial cells in patients with active GO may serve as a topical inflammation marker in Graves's orbitopathy.¹⁹

Elfenbein DM, et al. conducted a study on "Clinical and Socioeconomic Factors Influence Treatment Decision in Graves' disease" and the study concluded that the clinical factors are the main drivers behind treatment choice, but patients with lower socioeconomic factors are more likely to have clinical features best treated with surgery, underlying the importance of improving access to quality surgical care for all patients.²⁰

DISCUSSION: Orbital disorders are lesions of diverse aetiology and pathogenesis and can present with similar clinical picture, diagnostic and therapeutic algorithms would be simplistic and misleading.

Conclusions reached by any orbital survey vary according to the source of material and the age group studied. Percentage of biopsy proven entities, geographical area encompassed, the specialty and type of practice of the researchers, and the scope of diagnostic modalities used to evaluate the patient enrolled in the series. Two diagnostic modalities have revolutionized the scope and accuracy of orbital evaluation—USG and CT scan. Although the unequivocal diagnosis of orbital disease can be made only by histopathological examination, current noninvasive procedures can provide a correct general diagnosis in most cases.

We analysed 53 cases between November 2012 to June 2014, of which 13 cases were excluded as they met the exclusion criteria. The remaining 40 cases of Thyroid Orbitopathy were analysed and compared with other current data available from around the world.

One of the major studies in this part of the world was done at PGI, Rohtak by Khurana AK, Sunder S, Ahluwalia BK, Malhotra KC, Gupta S. A clinico-investigative profile in Graves' ophthalmopathy. Indian J Ophthalmol 1992; 40:56-58.²¹

Another study which was done in Lithuania is being compared with the present study. "Jankauskiene J, Imbrasiene D, Department of Eye Diseases, Kaunas University of Medicine, Eiveniu 2, 50009 Kaunas, Investigations of ocular changes, extraocular muscle thickness, and eye movements in Graves' ophthalmopathy. Medicina (Kaunas). 2006; 42(11):900-3."²²

Comparison criteria	Numbers and %'s in quoted study - PGI	Numbers and %'s in quoted study - Lithuania	Numbers and %'s in our study
No. of cases	30	27	40
Males	18(60%)	09(33.3%)	14(35%)
Females	12(40%)	18(66.6%)	26(65%)
Sex ratio(female:male)	2:3	2:1	2:1
Age range	17-50	-	18-67
Mean age	32.73	42	42
Peak occurrence	3 rd and 4 th decade	-	4 th decade
Hyperthyroid	63.3%	-	67.5%
Euthyroid	36.7%	-	25%

Most common muscle affected	Medial rectus > inferior rectus	Medial rectus > inferior rectus	Inferior rectus > medial rectus
Periorbital oedema	-	66.67%	60%
Chemosis	-	59.26%	60%
Congestion	-	45.15%	45%
Table 1: Comparison of other Studies with Our Study			

Analysing the main differences during comparisons were as follows: In other studies, medial rectus was the commonest muscle involved followed by inferior rectus whereas it was reverse in our study.

Our study was comparable to that of Lithuania study with the difference being number of cases which were more in our study, less incidence of periorbital oedema in our study and difference in muscle involvement as stated above.

When compared with the Rohtak study, there were a few differences. The female to male ratio in their study was 2:3 as compared to 2:1 in our study. The mean age of thyroid orbitopathy in their study was 32 years which was a decade lower than that in our study.

In addition, in our study, we analysed the data regarding periorbital oedema, lid retractions, motility defects, dry eyes and various other modes of presentations.

CONCLUSION: This clinical study of "Thyroid Orbitopathy" was carried in 53 consecutive patients attending Department of Ophthalmology at Owaisi Hospital and Research Centre, Kanchanbagh, Santhosh Nagar attached to Deccan College of Medical Sciences (DCMS) Hyderabad.

The following conclusion can be drawn from the study.

1. Of the 40 cases analysed, there was female preponderance noted. (Females- 65% whereas, Males-35%) and between age groups 25-50 years.
2. Based upon the thyroid status of the patients, they were subdivided into three groups namely: Hyperthyroid, Euthyroid and Hypothyroid. More than 65% of the patients were hyperthyroid followed by euthyroid in 25% and then hypothyroid in less than 10%.
3. The thyroid status was correlated with the sex of the patients. In both the sexes the hyperthyroid status (67.5%) was the most common followed by euthyroid (25%) and hypothyroid (7.5%). No male was reported to be hypothyroid.
4. It was found that lid retraction was (82.5%) the most common mode of presentation. The other clinical presentations were - Proptosis (57.5%), Periorbital swelling (62.5%), Congestion (45%), Chemosis (60%), Motility defects (10%), Diplopia (10%), and Dry eyes (12.5%).
5. Next, the laterality of orbitopathy was analysed. The most common presentation was bilateral (75%) than unilateral (25%).

6. The incidence of involvement of the various recti muscles was also analysed based upon ultrasonography and computed tomographic findings. It was found the inferior rectus (67.5%) was the commonest muscle involved followed by medial rectus (52.5%), superior rectus-LPS complex (27.5%) and lateral rectus (15%) in descending order.

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