Clinical outcomes of Graves ophthalmopathy

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Abstract
Aims: To quantify the clinical presentations, to study the complications and to quantify the response to different treatment modalities of Graves ophthalmopathy.
Materials and Methods: A retrospective study of 80 patients with Thyroid disorder who presented to Ophthalmology department of a tertiary health care centre in Kerala. All the patients were subjected to complete ocular examination which included Visual acuity, Tonometry, Colour vision testing, Hertels exophthalmometry, Slit lamp examination and Fundus examination. Clinical activity score of each patient at first visit was noted. All patients were specifically evaluated for exposure keratitis, lid signs and evidence of compressive optic neuropathy and secondary glaucoma.
Results: 58.8% were females. Lid retraction was the most common finding (63.75%). 52.50% had proptosis at presentation, of which 16.66% had severe proptosis. Among those with proptosis, 61.9% were males. 50% patients had Extraocular muscle involvement of which 2.5% showed involvement of all 4 recti muscles, 17.5% had 3 muscles, 37.5% had 2 muscles, 42.5% had single muscle involvement. 3.75% had optic nerve compression and 17.50% had glaucoma. 10% patients presented in active stage. 15% received intravenous methyl prednisolone, 3.8% underwent orbital decompression, 3.8% received radiotherapy and majority were managed conservatively.
Conclusion: Presentation of Graves ophthalmopathy varies from simple conjunctival congestion to vision threatening complication like optic nerve compression. Majority of patients presented in inactive stage. Those who presented in active phase and treated appropriately showed significant improvement, highlighting the need for prompt diagnosis and treatment of Graves ophthalmopathy when the disease is active.

Keywords: Graves ophthalmopathy, Proptosis, Dysthyroid optic neuropathy, Orbital decompression, Exposure keratopathy, Secondary glaucoma.

Introduction
Graves ophthalmopathy (GO) also known as Thyroid eye disease is an autoimmune inflammatory condition affecting eyelid, orbit, and eye. Clinical presentation varies from simple conjunctival congestion to complication like exposure keratopathy, optic nerve compression. Management depends on the activity of thyroid eye disease at the time of presentation. Medical records of patients diagnosed to have graves opthalmopathy were analysed. Clinical presentation, treatment methods and outcome are discussed in detail.

Aims of Study
1. Quantify the clinical presentations of Graves Ophthalmopathy (GO).
2. Study the complications of Graves Ophthalmopathy.
3. Quantify the response to different treatment modalities of Graves Ophthalmopathy.

Study Design and Setting
A list of 80 patients diagnosed to have Thyroid eye disease between the years 2008 to 2018 was obtained from Medical Records department of a tertiary health care centre in Kerala and analysed retrospectively.

Materials and Methods
All the patients underwent complete ocular examination which included Visual acuity, Tonometry, Colour vision testing, Hertels exophthalmometry, Slit lamp examination, fundus examination.

Clinical activity scores for all patients during each visit were noted. The patients were specifically evaluated for presence of exposure keratitis, lid signs, extraocular movement restriction, compressive optic neuropathy and secondary glaucoma.

The diagnosis of Graves ophthalmopathy (GO) was made if the patient had thyroid dysfunction along with one of the following: lid retraction, exophthalmos, optic neuropathy, or extraocular muscle involvement.

Thyroid dysfunction was noted when there was increased serum thyroxine (T4) or triiodothyronine (T3) levels, decreased serum Thyroid Stimulating Hormone (TSH) levels.

Extraocular muscle involvement was defined as extraocular movement restriction or objective evidence of enlarged muscles by orbital imaging.

Lid retraction was graded based on the position of upperlid margin relative to limbus. Upperlid margin at the limbus was considered as mild retraction, within 2 mm from the limbus as moderate retraction and more than 2 mm from limbus as severe retraction.

Proptosis was assessed using Hertels exophthalmometry, wherein value of 21 mm or more or a difference of 3 mm or more between the two eyes was considered as proptosis. Again, values between 21-23 mm was considered to be mild proptosis, 24-27 mm as moderate proptosis and more than or equal to 28 mm as severe proptosis.

The diagnosis of optic nerve dysfunction was based on abnormal visual acuity, colour vision, pupillary reaction, perimetry, disc edema or pallor.

Classification of Graves Ophthalmopathy (GO) was done according to the EUGOGO guidelines:

Sight-threatening GO

Patients with dysthyroid optic neuropathy (DON) and/or corneal exposure.

Moderate-to-severe GO

Patients whose eye disease has sufficient impact on daily life to justify the risks of immunosuppression (if active) or surgical intervention (if inactive). Patients with moderate-to-severe GO usually have any one or more of the following: lid retraction >2 mm, moderate or severe soft tissue involvement, exophthalmos >3 mm, inconstant, or constant diplopia.

Mild GO

Patients whose features of GO have only a minor impact on daily life insufficient to justify immunosuppressive or surgical treatment. They usually have only one or more of the following: minor lid retraction (< 2 mm), mild soft tissue involvement, exophthalmos upto 3 mm, transient or no diplopia and corneal exposure responsive to lubricants.

Clinical activity score was calculated by giving 1 score each to the following findings: chemosis, eyelid swelling, eyelid erythema, conjunctival congestion, caruncular swelling, pain in primary gaze, and pain with ocular movements. A score more than or equal to 4 was considered clinically active.

Secondary glaucoma was diagnosed when intraocular pressure was more than 21 mm Hg with or without glaucomatous optic disc changes or visual field defects.

Statistical Details

Continuous variables were represented as Mean +/- SD (Standard Deviation).

Categorical variables were represented as frequency and percentage.

Results

1. 58.8% patients were females and 41.2% were males.
2. Age Distribution - Mean age was 45.9 years, minimum age was 18 years and maximum 78 years.
3. 91% were hyperthyroid (52% of whom were diagnosed as Graves disease), 9% were hypothyroid.
4. 6.25% had Sight threatening disease, 13.75% had moderate disease and the rest (80%) had mild disease. (Table 1)
5. 52.50% (42 out of 80) had proptosis at presentation (59.52% had bilateral proptosis and 40.47% had unilateral proptosis), 16.66% had severe proptosis. Among those with proptosis 26 were males (61.9%) and 14 were females. Among those with severe proptosis all were males. 5 out of 7 patients, who had severe proptosis had secondary glaucoma.
6. Lid signs were seen in 63.75%, lid retraction being the most common among them. 58.82% had mild lid retraction, 23.52% had moderate lid retraction and 17.64% had severe lid retraction.
7. 50% patients had extraocular muscle involvement, 42.50% of whom had single muscle involvement (either inferior or medial rectus, majority being medial rectus), 37.50% had 2 muscle involvement, 17.50% had 3 muscle involvement and only 2.5% had involvement of all 4 recti muscles.
8. Medial rectus was the most commonly involved muscle (82.5%, 33/40) followed by inferior rectus which was involved in 70% (28/40), Superior rectus 10% (4/40), Lateral rectus in 7.5% (3/40).
9. 3.75% (3 out of 80) developed optic nerve compression. 2 of them were males. There was no association between optic nerve compression and severity of proptosis.
10. 17.5% developed secondary glaucoma, incidence equal among males and females. Glaucomatous disc changes were found to be associated with the severity of proptosis.
11. 10% (8 out of 80) had clinical activity score more than or equal to 4. Among them 6 were males and 2 were females.
12. 12 out of 80 patients (15%) received intravenous methyl prednisolone (IVMP) for treatment of active thyroid eye disease. 2 of them received IVMP for Dysthyroid Optic neuropathy before considering orbital decompression. After IVMP all of them showed improvement in clinical activity score by an average of 2. Decrease in proptosis was seen in 33% of patients by an average of 2 mm, 20% showed improvement in extra ocular movements. 2 out of 12 patients who received IVMP developed complications due to steroid therapy (central serous retinopathy), one of them showed recurrence of symptoms after stopping IVMP.
13. 3 out of 80 patients (3.8%) underwent radiotherapy. Indications were refractoriness to repeated courses of steroids for active disease and contraindication to steroids. They all showed improvement in clinical activity by an average of 2 and ocular movements, but no significant improvement in proptosis.
14. 9 out of 80 patients (11.25%) had taken Radioiodine therapy for hyperthyroidism, but none of them had exacerbation of orbitopathy after the therapy.
15. 3 out of 80 (3.8%) had to undergo orbital decompression surgery indications being severe vision threatening optic nerve compression and severe proptosis. Two of them had decrease in proptosis (by an average of 3 mm) following orbital decompression. Visual acuity and visual fields improved in all of them following surgical decompression.
16. 2 patients had exposure keratopathy and underwent lateral tarsorraphy. 3 patients underwent blepharoplasty.
17. Anti-Thyroid Peroxidase antibody levels were available for 32 patients, of which 11 had elevated titres. There was no correlation between the anti TPO levels and severity of the disease suggesting that there is no

association between Anti TPO level and severity of Graves ophthalmopathy.

Distribution of Ocular signs are shown in Table 2

Table 1: Distribution of severity of graves ophthalmopathy

Severity Level	Frequency	Percentage
Mild GO	64	80
Moderate GO	11	13.75
Sight threatening GO	5	6.25

Table 2: Graves ophthalmopathy - ocular manifestations

	Frequency	Percentage (%)
Lid Retraction	**51**	**63.75**
Mild	30	58.82
Moderate	12	23.52
Severe	9	17.64
Extraocular muscle involvement	**40**	**50**
4 muscles	1	2.50
3 muscles	7	17.50
2 muscles	15	37.50
Single muscle	17	42.50
Proptosis	**42**	**52.5**
Unilateral	17	40.47
Bilateral	25	59.52
Mild	24	57.14
Moderate	11	26.19
Severe	7	16.66
Optic Nerve Compression	**3**	**3.8**
Secondary Glaucoma	**14**	**17.50**

Discussion

Graves Ophthalmopathy (GO) also known as Thyroid eye disease is an autoimmune inflammatory condition associated with clinical findings of exophthalmos, restrictive myopathy and eyelid retraction.[1] In a study conducted by Bartley GB et al, the overwhelming majority (90%) of thyroid eye disease cases were associated with hyperthyroidism, while the rest are either euthyroid or hypothyroid.[2] In our study 91% were hyperthyroid and the remaining 9% were hypothyroid.

Cross reactivity against shared antigen(s) in thyroid and orbital tissue is most likely responsible for the autoimmune reaction. Antibodies involving the thyroid-stimulating hormone (TSH) receptor may drive the pathogenesis of this inflammation.[2]

Lid retraction is the most common abnormality associated with GO documented in up to 90%.[3] In our study lid retraction was the most commonly seen abnormality (63.75%). Putterman and Urists suggest that a synkinesis of the superior rectus and levator muscles to overcome inferior rectus muscle restriction may frequently cause lid retraction.[4] Increased sympathetic tone acting on Müller's muscle is another cause for lid retraction.[5]

According to Neepa M. Thacker MD[a] et al, recti muscles involvement in decreasing order frequency are the inferior, medial, superior, and lateral recti.[6] In our study, we found medial rectus as the most commonly involved muscle may be because it is the bulkiest of extra ocular muscles due to its constant use in convergence.

Radioactive Iodine (RAI) is frequently used as treatment for Graves disease associated hyperthyroidism. RAI causes necrosis, atrophy, and fibrosis of thyroid follicular cells.[7] Following treatment with RAI, there is transient increase of TSH-R antibodies (TRAb) and Thyroid Stimulating Immunoglobulin.[8] Although RAI is considered as a risk factor for both development and progression of GO,[7,8] our study did not show any worsening of Graves ophthalmopathy with RAI, may be because all of them had received oral Prednisolone 1 mg/kg/day for 3 days prior to RAI ablation tapering every 3 days after the procedure.

Mild Thyroid eye disease was managed with Lubricants and oral supplementation of Selenium, 100 μg twice daily for 6 months, which is an anti-oxidant. Selenium helps by suppressing the Reactive Oxygen Species in the orbit, which contribute to the pathogenesis of Thyroid eye disease.

Intravenous Methyl Prednisolone (IVMP) was given to all active cases of moderate to severe Thyroid eye disease. The regimen followed was 0.5 g/week for a period of 6 weeks followed by 0.25 g/week for another 6 weeks,[9] so that the cumulative dose never exceeded 4.5 g in one course of therapy. Intravenous Glucocorticoids are safe if the cumulative dose is 8 g methylprednisolone in one course of therapy.[10] In our study, 15% received IVMP, the majority of which were indicated as treatment for active disease, 2 of them also received IVMP for Dysthyroid Optic neuropathy before considering obital decompression. After IVMP all of them showed improvement in clinical activity score, 33% showed decrease in proptosis, 20% showed improvement in extra ocular movements. Literature review shows that randomized studies, in which Glucocorticoids were compared with other treatments[11-13] show a favourable response in 33–63% of patients, particularly for soft tissue changes, recent onset eye muscle involvement and DON (Dysthyroid Optic Neuropathy), the findings are at par with that of our study.

Very severe TO can occur in 5% to 10% of patients, resulting in DON and possible blindness. The prevalence of Compressive optic neuropathy in our study was 3.8% (3 out of 80 patients). Glucocorticoids (GCs), surgical decompression of the orbit are the treatments proved to be effective in patients with DON. Intravenous methylprednisolone was started first in our patients with DON, the response noted, if not good a repeat IVMP course was tried before resorting to decompression surgery or radiotherapy.

In our study group, none of the patients with severe proptosis had Optic nerve compression. The absence of association between severity of proptosis and optic nerve compression can be explained by the fact that development of exophthalmos may prevent compressive optic neuropathy by relieving soft tissue crowding of the

orbital apex when tissue is allowed to reposition in an anterior direction.[14]

The results of radiotherapy was in accordance to that of the study conducted by Yao Wang, MD et al.[15] Following radiotherapy there was improvement in extraocular muscle movements and diplopia, other soft tissue manifestations, including proptosis and eyelid retraction, did not change significantly.[16,17] Radiotherapy dosage followed in our centre -is 20 Gy (Gray) in 10 fractions, given as 200 cGy per fraction, 5 fractions per week. Technique: 3DCRT (3D conformal Radiotherapy) with opposed right and left laterals or Intensity modulated radiotherapy. In the lens region, the dosage of radiation is reduced to 10 Gy.

Rehabilitative surgery should only be performed in patients who have had inactive GO for at least 6 months. Surgical management should proceed in the following sequence: orbital decompression, then squint surgery and then lid lengthening with or followed by blepharoplasty/ browplasty, since side effects of the preceding step can interfere with the step that follows.[18]

Only 3.8% of our patients had to undergo surgical orbital decompression, the indications being severe vision threatening compression and severe proptosis. 2 of them had decrease in proptosis following the same. Visual acuity and visual fields improved in all of them following decompression. In a study conducted by Mehmet Ozgur Cubuk et al, around 30% of orbital decompression surgeries were for DON, whereas the majority (around 70%) were indicated for cosmetic reasons. Whereas our patients underwent decompression surgery for vision threatening optic neuropathy and severe proptosis, none of them were for cosmetic reasons.

Initially, orbital decompression surgery was primarily performed on patients with visual compromise, orbital pain, steroid dependency, or severe ocular surface disease due to exposure.[19] However, indications have evolved, and orbital decompressions are patient-specific ranging from primarily aesthetic to functional concerns and preparation for other rehabilitative procedures like strabismus and/or eyelid surgery.[20] The primary goal of orbital decompression surgery is to increase the effective volume of the orbit. Orbital decompression in the active phase is typically reserved for patients with evidence of proptosis resulting in exposure keratitis refractory to conservative measures and optic neuropathy.[21]

Bony decompression may be achieved by targeting individual orbital walls or combinations of the lateral wall, medial wall, orbital roof or floor. Orbital fat can be excised either with or without bony decompression using a variety of techniques. In cases of DON, the goal is to reduce orbital congestion at the apex and improve vascular perfusion within the optic nerve. Studies have demonstrated that increasing the number of walls decompressed yields a greater reduction in proptosis, though with greater morbidity.[21]

Secondary glaucoma in thyroid eye disease (TED) is attributed either to raised episcleral venous pressure or to mechanical compression induced trabecular meshwork damage by mucopolysaccharide deposition. In a study conducted by Cockerham KP et al 24% of Thyroid eye disease patients were found to have IOP more than 22, whereas it was 17.50% in our study.[22,23] All of them were managed with topical anti glaucoma medications(aqueous suppressants), none of them required surgery.

Conclusion

The prevalence of Graves ophthalmopathy though found more in females, complications were observed more in males. The presentation varied from simple conjunctival congestion to complications like optic nerve compression. Majority of patients presented in inactive stage. Those who presented in active phase and treated appropriately showed significant improvement, highlighting the need for prompt diagnosis and treatment of Graves ophthalmopathy when the disease is active.

Conflict of Interest: None.

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