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A Clinical study on Thyroid Eye Disease conducted in Government General Hospital ,Guntur

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Abstract:
Background*: Thyroid eye disease is the most common cause of unilateral or bilateral proptosis in adults. It is the most important extra thyroidal manifestation of autoimmune thyroid diseases such as Graves' disease and Hashimoto's thyroiditis.*
The five main clinical manifestations of Thyroid Eye Disease (TED) are
(a) Soft tissue involvement
(b) Lid retraction
(c) Proptosis
(d) Optic neuropathy
(e) Restrictive myopathy
As there are sight threatening lesions in thyroid eye disease, this study was undertaken to identify them and give appropriate management.
Materials and Methods*: The current study is an observational cross sectional study conducted over a period of 2 years in a sample of 69 patients attending to Out Patient Department, Government General Hospital, Department of Ophthalmology, Guntur.*
Results*: In the present observational cross sectional hospital based study conducted over a period of 2 years,69 patients were included after satisfying the inclusion and exclusion criteria who were attending the outpatient department of Ophthalmology, Government General Hospital, Guntur. All of them were subjected to detailed ophthalmic examination and other investigations were done as required. Majority of the cases were in the age group of 41-50 years. There was a female preponderance with female:male ratio with 2.43:1,*
smoking and high TSH levels were found be associated risk factors but found in only less number of patients but smoking is associated with increase in severity of disease. There was a bilateral presentation in most of the Cases. Majority of the patients were hyperthyroid at the time of presentation, euthyroid and hypothyroid patients were seen less in number. Onset of TED followed the onset of Graves disease in most of the patients with mild disease being common in most of the patients. Eyelid signs were seen in almost all the patients but the most common ocular manifestation is exophthalmos followed by eyelid retraction. Soft tissue involvement, extraocular muscles and corneal involvement was much less common. Optic neuropathy was not observed in any case.
Conclusion: *The most common ocular manifestation is exophthalmos followed by eyelid retraction. Females were most commonly affected but disease being severe in males with majority of the cases presenting in 41-50 years of age group. The onset of thyroid eye disease followed the onset of Graves disease in most of the cases but statistically insignificant with P-Value 0.55.Smoking is associated with severity of disease with P Value 0.00001.*
Key Word*: Thyroid Eye Disease(TED) Soft tissue involvement, Lid retraction , Proptosis , Optic neuropathy , Restrictive myopathy*

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I. Introduction

Thyroid eye disease is the most common cause of unilateral or bilateral proptosis in adults. It is the most important extra thyroidal manifestation of autoimmune thyroid diseases such as Graves' disease and Hashimoto's thyroiditis.

The five main clinical manifestations of Thyroid Eye Disease (TED) are (a) Soft tissue involvement (b) Lid retraction (c) Proptosis (d) Optic neuropathy (e) Restrictive myopathy has documented the efficacy.
RISK FACTORS:
A) Age and Gender :Graves' Orbitopathy (GO) is most prevalent in women and most severe in men[1]. There is an association between severity of thyroid- associated ophthalmopathy and advancing age and male gender.
B) Smoking :Cigarette smoking has been considered the strongest risk factor for developing TED[2]
C) Others include [3]
- Severe hyperthyroidism
- Elevated TSH-receptor antibodies
- Elevated TSH levels
- Radioiodine
- Late correction of hypothyroidism
- Preexisting orbitopathy

II. Material And Methods

This observational study was carried out on patients of Department of ophthalmology at Government General Hospital, Guntur ,Andhra Pradesh from January 2019 to January 2020. A total 69 adult subjects (both male and females) of aged 40 to 50 years were for in this study.
Study Design: Observational study
Study Location: This was a tertiary care teaching hospital based study done in Department of ophthalmology,at Government General Hospital, Guntur ,Andhra Pradesh
Study Duration: January 2019 to January 2020
Sample size: 69 patients.
Inclusion criteria:
1. Patients with either sex with symptoms and signs suggestive of thyroid disease and their ocular manifestations.

Exclusion criteria:
1. Patients with other causes of proptosis.
2. Patients who underwent eyelid surgeries.
3. Patients with other co-morbid debilitated diseases.

Procedure methodology

After obtaining approval of the Institutional Ethics Committee, a written/ informed consent was taken from patients in his/her vernacular language. A thorough clinical history was taken regarding chief complaint, duration of disease and any other relevant history. A complete ophthalmic examination of the patients was done at presentation including visual acuity, anterior segment examination with slit lamp, eyelid examination, intra ocular pressure measurement, fundoscopy, gonioscopy, exophthalmometry, ocular movement examination.
Other tests done as per requirement:
• Thyroid profile
• Perimetry
• X-ray orbits
• CT-orbits
• B-Scan ultra sound orbits
• Fundus photography

III. Result

In our study majority of the cases are 43 females (62.31%) and 26 males (37.68%) and most of the cases are in the age group 41 to 50 years .Majority of the patients have a visual acuity between 6/6 – 6/18 and none had developed no perception of light. Majority of patients had a bilateral disease.

Table no 1 : Associated risk factors on males and females

	MALES	FEMALES	TOTAL
Current Smokers	19	3	22
Non Smokers	7	37	44
High TSH levels	0	3	3
Total	26	43	69

Only 31.88% of patients included in the study were smokers. Among the current smokers, majority (86.36%) were males. Among the non-smokers, most of the patients were females (84.09%).

Table no 2: Thyroid status at the time of presentation.

THYROID STATUS	NUMBER OF CASES	PERCENTAGE
Hyperthyroid	**51**	**73.91**
Euthyroid	**6**	**8.69**
Hypothyroid	**12**	**17.39**
Total	**69**	

Majority (73.91%) of patients were hyperthyroid at the time of presentation.
8.69 % were euthyroid and 17.39 % were hypothyroid.

Table no 3 : Ocular symptomatology

OCULAR COMPLAINTS	NUMBER OF PATIENTS
Grittiness/ FB sensation	26
Redness and watering	11
Double vision	1
Visual loss	2

The most common complaint was grittiness/foreign body sensation (37.68%) followed by redness and watering (15.94%). Diminution of vision was complained of by only 2.89% patients**.**

Table no.4 :Ocular signs

OCULAR SIGNS		NUMBER OF PATIENTS
Lid retraction (Dalrymple's sign)	Upper eyelid	31
	Lower eyelid	16
Lid lag (Von graefe's sign)		16
Lid fullness (Enroth's sign)		7
Infrequency of blinking		6
(Stellwag's sign)		
Lagophthalmos		8
Conjunctival injection (Goldzeihers's sign)		14
Convergence weakness (Moebius sign)		7
Extraocular muscle restriction		4

Most common lid sign seen among the patients included in the study is eyelid retraction .seen in 68.11% of patients

Table no 5 : Ocular manifestations

	Number of patients
Eyelid retraction	47
Exophthalmos	49
Soft tissue involvement	20
Extra ocular motility restriction	4

Corneal involvement	2
Optic nerve involvement	0

The most common ocular manifestation in the present study is exophthalmos seen in 71.01 % of patients.

Table no 6: Severity of proptosis of the most affected eye

SEVERITY OF PROPTOSIS	NUMBER OF PATIENTS
Mild (21 -23 mm)	25
Moderate (24 – 27 mm)	34
Severe (28 or more)	0

Most of the patients are manifesting moderate amount of proptosis

Table no 6 : Disease activity according to clinical activity score

Disease activity	Number of patients
Clinically active	8
Inactive	61
Total	69

Disease is clinically inactive in most of the cases

Tabel no :7 Grading the cases according to NOSPECS classification

CLASS	**Number of patients**
CLASS 0	0
CLASS 1	20
CLASS 2	7
CLASS 3	59
CLASS 4	4
CLASS 5	2
CLASS 6	0

IV. Discussion

Thyroid eye disease is the most common cause of unilateral or bilateral proptosis in adults. It is the most important extra thyroidal manifestation of autoimmune thyroid diseases such as Graves' disease and Hashimoto's thyroiditis.

The five main clinical manifestations of Thyroid Eye Disease (TED) are (a) Soft tissue involvement (b) Lid retraction (c) Proptosis (d) Optic neuropathy (e) Restrictive myopathy has documented the efficacy.

PATHOGENESIS :

A feature common to nearly all individuals with Graves' Disease (GD) is the presence of activating anti-TSH receptor antibodies (TSHR)[4]. The TSHR- directed antibodies produced subsequently may reflect the intensity of the orbital autoimmune response[5].

Orbital pathology in TAO results from infiltration of tissues by immunecompetent cell predominantly CD4+ T lymphocytes exhibiting an activated memory phenotype and numerous granulated mast cells in the extraocular muscle interstitial tissue, orbital fat and connective tissue[6]. The perimysial tissue contains excessive GAG composed of hyaluronan and chondroitin sulfate[7]. The fibroblast is an important source of hyaluronan[8]. Fibroblasts both respond to and produce numerous molecular mediators that serve to activate and modulate the behavior of bone marrow-derived cells and provoke their migration to sites of inflammation. Orbital fibroblasts exhibit exaggerated responses to proinflammatory signals such as those conveyed by cytokines. Leukoregulin, a T cell-derived cytokine, up-regulate several proinflammatory orbital ―fibroblasts‖ genes, including the cyclooxygenases (COX-2) and therefore the production of prostaglandin E2 (PGE2). In addition, the induction of IL–6, IL–8, tissue inhibitor of metalloproteinases, and the three mammalian hyaluronan synthases is exaggerated.

Orbital fibroblasts, those associated with extraocular muscles uniformly display Thy-1. Thy-1+ orbital fibroblasts generate higher levels of PGE2 and exaggerated expression of prostaglandin endoperoxide H synthase (PGHS)-2, also known as COX-2, the inflammatory cyclooxygenase, in response to IL-1beta. Thy-1– orbital fibroblasts express higher levels of IL-8. They differentiate in vitro into mature adipocytes when subjected to cAMP-enhancing agents. The adipogenic potential in Thy- 1– orbital fibroblasts has substantial implications for the pathogenesis of TAO, since expansion of orbital fat is a prominent feature of the disease.

Cytokines appear to play a major role in thyroid associated ophthalmopathy. There is infiltration of extraocular muscles by activated T cells, the release of cytokines such as Interferon – gamma, Tumour necrosis factor and Interferon – 1 results in fibroblast activation and increased synthesis if glycosaminoglycans that trap water, thereby leading to characteristic muscle swelling. Late in the disease, there is irreversible fibrosis of the muscles. Orbital fibroblasts may be particularly sensitive to cytokines, perhaps explaining the anatomic location of the immune response. Though the pathogenesis of thyroid associated ophthalmopathy remains unclear, there

is mounting evidence that the TSH-R may be a shared autoantigen that is expressed in the orbit, this would explain the close association with autoimmune thyroid disease. Increased fat is an additional cause of retrobulbar tissue expansion. The increase in intraorbital pressure can lead to proptosis, diplopia and optic neuropathy[9].

CLINICAL MANIFESTATIONS :The clinical features include soft tissue involvement, exposure keratopathy, extraocular motility disturbances, eyelid signs, exophthalmos, optic Neuropathy

SOFT TISSUE INVOLVEMENT : Symptoms are variable grittiness, photophobia and lacrimation. The most characteristic signs are eyelid erythema and swelling, caruncular and conjunctival swelling (chemosis). Fluctuating upper or lower eyelid swelling indicates active disease while chronic swelling in the absence of erythema suggests congestive ophthalmopathy. Diminished tear production results from lacrimal gland infiltration.Other signs include resistance to retropulsion, injection over the horizontal rectus muscle insertions (Goldzieher's sign).

EXTRAOCULAR MOTILITY RESTRICTION: The extraocular muscles appear to be the primary area of orbital involvement. severe TAO can present as dysfunctional eye motility. Limited eye movements are usually associated with diplopia in the corresponding fields of gaze, causing vertical diplopia when inferior rectus is involved. Motility restriction is either due to the presence of lymphocytic infiltration and edematous swelling (active disease) or fibrosis (inactive disease) in the muscles. Typically, limitations of elevation follow those of abduction. Correspondingly, involvement of the inferior, medial, superior, and lateral rectus muscle are encountered in decreasing frequency[10-12]. Most patients with TAO, including those with no evidence of ocular motility abnormalities, exhibit some degree of extraocular muscle involvement demonstrable by radiographic techniques[13-15.] Elevated intraocular pressure in the primary position or on upgaze can accompany TAO, often related to either restrictive myopathy or orbital congestion[16-19]. This results from the pull of an inelastic inferior rectus muscle on the eye. It can be demonstrated on attempted upgaze[20.]

CORNEAL INVOLVEMENT: Exposure keratitis occurs in patients with TAO for several reasons. Inadequate eyelid closure, the consequence of proptosis and eyelid dysfunction, contributes to excessive moisture loss. A careful slitlamp examination using fluorescein stains allows identification of exposure. Rarely, severe exposure keratitis can result in corneal thinning, ulceration and perforation. Another feature is superior limbic keratitis, which is characterized by a fine, nodular, superior pannus with slight keratinization of the epithelium. This may occur as a result of lid retraction. It is associated with localized injection and. significant symptoms of irritation and foreign body sensation, and there is frequently evidence of adjacent filamentary keratitis.**EYELID SIGNS**:

Sign	**Description**
Abadie's sign	Elevator muscle of upper eyelid is spastic
Boston's sign	Jerky movements of upper lid on lower gaze
Darlimple's sign	Upper eyelid retraction
Enroth's sign	Edema of the lower eyelid
Gifford's sign	Difficulty in eversion of upper lid.
Griffith's sign	Lower lid lag on upward gaze
Jellinek's sign	Superior eyelid folds is hyperpigmented
Kocher's sign	Spasmatic retraction of upper lid on fixation
Pochin's sign	Reduced amplitude of blinking
Riesman's sign	Bruit over the eyelid
Rosenbach's sign	Eyelids are animated by thin tremors when closed
Snellen-Rieseman's sign	When placing the stethoscope's capsule over closed eyelids a systolic murmur could be heard
Stellwag's sign	Incomplete and infrequent blinking
Tellas's sign	Inferior eyelid might be hyperpigmented
von Graefe's sign	Upper lid lag on down gaze

EXOPHTHALMOS: TED is the most common cause of unilateral and bilateral proptosis in adults.. Bilateral exophthalmos is seen in approximately 85% of cases. Unilateral proptosis reflects asymmetric muscle involvement and is less commonly seen (10 – 15% of patients). The onset of exophthalmos is usually gradual and insidious, although in some cases it can be stormy or ―malignant.‖ It can be quantified by the exophthalmometer or radiologically with axial orbital scans.

OPTIC NEUROPATHY: Visual loss rarely complicates TAO and usually results from compressive optic neuropathy. Optic neuropathy occurs in ~5% of individuals with TAO and affected individuals usually do not exhibit marked proptosis or optic nerve changes under ophthalmoscopic examination[21-22]. Risk factors for optic neuropathy include older age, smoking, male gender and significant strabismus with mild proptosis[23]. Typically, acuity and colour perception are slightly decreased with a questionable afferent pupillary defect and vague visual-field defects, while the optic disc appears entirely normal to clinical examination[24]. Less commonly, optic nerve edema and peripapillary hemorrhages occur. Patients developing optic neuropathy may develop late nerve

atrophy and irreversible visual loss. It is caused by compression of the optic nerve from the enlarged extraocular muscles as they approach the posterior orbit and the annulus of Zinn. Either direct pressure to the nerve or restriction in the arterial blood flow through the optic nerve causes the damage.

V. Conclusion

Currently, a thorough understanding of the molecular basis of thyroid eye disease has allowed for earlier diagnosis with more accurate prognostication. Much research still needs to be done, however, since it's unclear exactly which factors trigger the onset of TED in a patient with Graves hyperthyroidism. Elucidating these factors may allow accurate prediction and allow for earlier treatment.

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