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Clinical Profile of Thyroid Associated Ophthalmopathy and Relationship of Exophthalmos to Serum T3,T4 Status

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Abstract

Introduction: *The ocular symptoms may be the first manifestation in an endocrine disorder of thyroid. The ocular manifestations are frequent in hyperthyroid Graves disease but rarely associated with Hashimotos disease, thyroid carcinomas and euthyroid states. Euthyroid patients with TAO, eventually develop subtle or overt fluctuations in thyroid function.*

Aim *1. The various ocular manifestatons of thyroid disorders were examined and the relationship of Graves exophthalmos to serum T3,T4 was studied.*

Materials and Methods: *A prospective study of 50 patients with TAO above 18 years were done over a period of 18 months with detailed ocular workup including measurement of proptosis with Hertels exophthalmometer. Routine investigations and thyroid function test were done. Stastical analysis was done using SPSS version 11. Clinical profile is presented in %. Association of the different grades of ophthalmopathy with T3T4 levels was analysed using student t- test. .*

Results: *The most common ocular manifestation was lid retraction i.e in 35 (70%) cases. This was closely followed by proptosis i.e 33 (66%) cases. Ocular myopathy occurred in 22(44%) cases. The most common ocular symptom was grittiness and burning sensation.(48%). 3 (6%)cases had optic nerve involvement. The mean levels of serum T3(p=0.605) and T4(p=0.548) were not significantly different in different degrees of exophthalmos.*

Conclusion: *TAO is a common ocular entity in a patient who may present to ophthalmologist in a referral centre. Our role lies both in diagnosing the ocular malady and treating it as well as directing the patient for evaluation and treatment of systemic manifestations of the disease at the earliest.*

Absence of definite association between T3,T4 levels and exophthalmos and its occurrence even in hypothyroid states supports immunological pathogenesis. Lab investigations are helpful to diagnose and monitor treatment aspects but newer investigative modalities are yet to be devised as definite markers of TAO.

Keywords: *thyroid ophthalmopathy, exophthalmos, graves.*

INTRODUCTION

TAO is an autoimmune disorder with characteristic clinical signs and symptoms with significant functional and cosmetic consequences. Twenty percent of patients state that ocular morbidity of TAO is more troublesome than systemic problems.

The usual disorders of thyroid with ocular manifestations include Graves disease, Hashimotos disease, thyroid cancer, thyroiditis. Of course, Graves is the most commonly associated condition. Ophthalmopathy is clinically apparent in approximately 50% of Graves patients. Euthyroid patients who present with ocular manifestations are termed ophthalmic graves[1.]; where orbitopathy is less severe. Lab investigations are helpful to diagnose and monitor the treatment aspects. Dysthyroid patients have some detectable ophthalmopathy and patients with TAO, eventually develop subtle or overt fluctuations in thyroid function.

MATERIALS AND METHODS

A prospective study of 50 consecutive patients with TAO were done at our outpatient department in association with department of endocrinology, Government Medical college for a period of 18 months.

Age and sex of patients were noted, those above 18 years were included. A detailed history of symptoms were taken which included resting and gaze evoked pain, defective vision, redness, diplopia, photophobia, puffy lid and headache.

The treatment history was also noted. Patients not on treatment were sent for thyroid status evaluation at endocrinology clinic.

Examination of lid signs like lid retraction, lid lag, edema and redness of eyelids were noted. Soft tissue involvement as conjunctival chemosis, swelling of caruncle and protrusion of orbital fat were noted. Corneal involvement of punctate lesions and ulceration were noted. IOP was measured using applanation tonometer. Extraocular movements assessed and pattern of ocular myopathy observed.

Forced duction test, diplopia charting were done in selected cases. The measurement of unilateral and bilateral proptosis was done using Hertels exophthalmometer. The normal measurement was assumed according to a study of exophthal-mometric values in normal Indian population by Punita Kumari Sodhi as: for male's right eye (12.43+0.25) x age, left eye (12.30+0.029) x age and females right eye (13.30-0.003) X age, left eye (13.17-0.003) x age and maximum measure-ment taken[2]. 3 mm and less was considered mild and more than 3mm was considered moderate to severe exophthalmos. Serum T3,T4,TSH was done in all cases. Association of serum T3 and T4 to mild and moderate to severe proptosis were studied in hyperthyroid patients.

Visual acuity, color vision and presence of relative afferent pupillary defect was noted and it was followed by fundus evaluation to look for signs of optic nerve compression. HFA C-30-2 were done in affected cases. CT scan, USS B scan, MRI and antithyroid antibodies were done in selected cases. Patients with neurological disorders and myasthenia gravis were excluded from study. Statistical analysis was doneusing SPSS version 11. Clinical profile is presented in %. Association of the different grades of ophthalmopathy with T3T4 levels was analysed using student t- test.

RESULTS

In this study of 50 cases of TAO the maximal incidence was found in fifth decade. Lowest incidence was below third decade of life.76% were females, with an approximate ratio of female:male of 3:1. 6% of 50 cases belonged to euthyroid, 8% were hypothyroid in nature and rest hyperthyroid. TAO doesn't confine to hyperthyroid status since circulating antibodies may act as the determinant factor.

In this study, 33 cases ie 66% showed exophthalmos. Out of 33 cases, 29 cases were hyperthyroid, 2 had hypothyroid,2 had euthyroid status.

Lid retraction was noted in 70% of cases ie 35 cases.3 cases had euthyroid and 3 had hypothyroid status and rest 29 were hyperthyroid. Out of 29 cases,5 cases had unilateral involvement.

The most common ocular manifestation was lid retraction (70%) closely followed by exophthalmos (66%).

A fairly good (44%)number of cases showed extraocular muscle involvement, inferior rectus in 20 cases, medial rectus in 17, incidence of lateral and superior rectus were identical, 5 cases each. Only one case was euthyroid and one was hypothyroid, 20 cases had hyperthyroid status.

Apart from proptosis, the most common ocular presenting symptom was grittiness and burning sensation.(48%) Corneal involvement was noted in 4 i.e 8%cases.In the study,3 cases had optic nerve dysfunction i.e 6%.

An association between serum T3 and T4 levels and appearance and severity of exophthalmos was not noted.

Table 1.Clinical Profile of TAO

CLINICAL FEATURE	NO:OF PATIENTS	PERCENTAGE
Lid retraction	35	70
Lid lag	16	32
Chemosis	9	18
Grittiness	24	48
Ocular myopathy	22	44
Proptosis	33	66
Optic neuropathy	3	6

Table 2 Pattern of Ocular Myopathy

Muscle involved	No:of patients	%
Inferior rectus	20	40
Medial rectus	17	34
Superior rectus	5	10
Lateral rectus	5	10

Table 3.Thyroid Profile of TAO

Clinical feature	total	Hyperthyroid	Euthyroid	hypothyroid
exophthalmos	33	29	2	2
Lid retraction	35	29	3	3
myopathy	22	20	1	1

Table 4. Stastical Analysis for Association of Serum T3,T4 to Exophthalmos in Hyperthyroid Patients.

	Exocat	N	Mean	Std. Deviation	Std. Error Mean	T value	P value
T4	1	26	15.854	14.7185	2.8865	.605	.548
	2	24	13.872	6.6142	1.3501		
..Serum T3	1	26	263.88	113.501	22.259	.520	.605
	2	24	280.50	112.003	22.862		

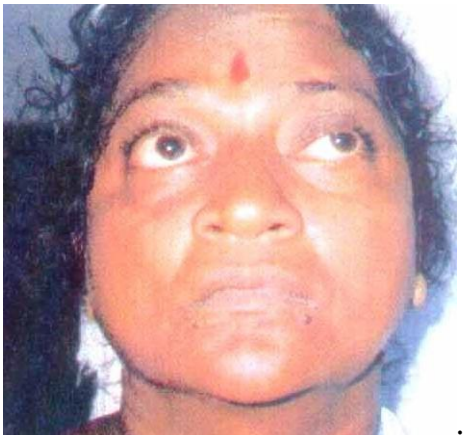

Figure 1.ocular myopathy involving inferiorrectus presenting as restriction of elevation.

Figure.2 bilateral severe exophthalmos and lid retraction in a hyperthyroid patient.

DISCUSSION

Thyroid associated orbitopathy frequently termed Graves ophthalmopathy is an organ specific autoimmune process associated strongly with dysthyroidism. TAO may precede, coincide or follow the systemic complications of dysthyroidism[3]. TAO is an autoimmune mediated disorder where thyroid stimulating hormone receptor act as an effective autoantigen with resultant raised TSH-R antibody levels and expression[4]

Euthyroid ophthalmopathy occur in 10% of presumed thyroid eye disease.[5] This study had 6% incidence.

The maximal incidence was noted in 5th decade of life.TAO was 3 times more common in females (76%).

Various studies suggest that TAO affects women 2.5-6 times more frequently than men[6].Severe

cases of TAO occur more often in men than women and tend to be more frequent in patients older than 50 years.[7]

TAO mostly affect patients aged 30-50 years.

In this study 70% had lid retraction of which 5 were unilateral and all were hyperthyroid.3 cases each had euthyroid and hypothyroid status. This can be compared to other similar studies.[3,5]Upper lid retraction is caused by levator/mullers muscle inflammation and fibrosis or levator overaction secondary to inferior rectus restriction.

In this study, 33 cases i.e 66% showed exophthalmos. Out of 33 cases a significant number (62.5%) was bilateral axial in nature. Exophthalmos was as frequent as 62% in another study [5].Exophthalmos occur due to expansion of orbital fat and muscles. It is a characteristic finding in TAO, occurring in 34% to 93% of patients.

The study had a 6%incidence of optic neuropathy. Dysthyroid optic neuropathy is due to compression at orbital apex by enlarged EOM[10].It is a rare complication[4] as reported by other studies. In this study all three were males and were hyperthyroid. One was 49 years and other 2 were sixty years of age. Dysthyroid optic neuropathy is more frequent in elderly, male and diabetic patients[7]. CT helps to demonstrate enlarged

EOM at orbital apex.MRI with diffusion weighted imaging has recently been proven to be useful in the objective assessment of activity in Graves ophthalmopathy patients. Chemosis was noted in 18% of patients in this study. Compression in orbitalspace impaires venous drainage leading to chemosis.

The association of exophthalmos to serum T3 showed no significance (p value=0.605). There was no significant association between serum T4 and exophthalmos (p=0.548).

Actions of several cytokines andmolecular interplay peculiar to the orbit appear to provoke the inflammation, fat expansion, and deposition of excessive extracellular matrix molecules [8].The consequences are fibroblastic proliferation whose high osmotic pressure and polyanionic charge imbibe water and EOM swells up. The volume of orbit is also increased by hyperplasia of adipose tissue.The compression in orbitalspace impaires venous drainage leading to chemosis. Graves ophthalmopathy follows a biphasic course with initial active phase of progression followed by subsequent partial regression phase of inactivity.

In 1969, NO SPECS classification was adopted. But later Mourits et al described Clinical Activity Score (CAS) based on signs of acute inflammation[11]. For initial CAS only score 1-7[11].

1. spontaneous orbital pain
2. gaze evoked orbital pain
3. eyelid swelling due to active GO.
4. eyelid erythema
5. conjunctival redness
6. chemosis
7. inflammation of caruncle or plica Patients assessed after follow up(1-3/12) can be scored out of 10 by including 8-10
8. increase in 2mm proptosis.
9. Decrease in uniocular ocular excursion in anyone direction of >8 degree
10. decrease in snellen acuity 1 line

Active Graves ophthalmopathy if >=3/7 in first exam or >4=10 /12 in successive exams.

EUGOGO classification for severity differentiate mild being <2mm lid retraction,<3mm proptosis, corneal exposure responding to lubricants, mild soft tissue involvement, no/transient diplopia. Moderate to severe cases include worse situations including inconstant/constant diplopia.

VISA classification refers to Vision, Inflammation, Strabismus, Appearance/Exposure[10.]

Restrictive ocular myopathy occurred in 44% which can be comparable to other study(43%) by Bartley GB[12].The pattern of ocular myopathy involve inferior, medial, superior, lateral and obliques in a predictable fashion with sparing of tendinous insertions. our study had similar pattern but superior and lateral rectus had similar incidence of 10%.40% had inferior rectus involvement and 34% had medial rectus involvement.

Although most cases of TAO can be managed medically and without visual loss,it may result in

vision threatening exposure keratopathy and compressive optic neuropathy hence important to recognize TAO.

In our study apart from proptosis, commonest presenting symptom was gritting sensation experienced by 48% patients. TAO patients often complain of symptoms like puffy eyelids, dry eyes, angry looking or bulging eyes, diplopia, visual loss, dyschromatopsia, photopsia on upgaze, pain.

Lid signs described are Dalrympe sign (upper lid retraction), Vongraefe sign(upper lid lag on downgaze), Griffith sign(lower lid lag on downgaze), Stellwag sign(incomplete and infrequent blinking), Groves sign(resistance to downward pull of upper lid),. Gifford (difficult eversion of upper lid) Gellineks (abnormal pigmentation of upper lid), Kochers (spasmodic retraction of upper lid during fixation) Boston (uneven jerky motion of upper lid on inferior movement) Enroth (lower lid edema) Vigoroux (puffiness of lids). Joffroy (absent creases on forehead on superior gaze). others are ptosis, pseudoptosis, deep glabellar rhytids.

Conjunctival signs include a deep injection especially temporally which suggests increased tissue pressure and venous stasis due to disease activity.

Superior limbic kerato conjunctivitis of Theodore is characterized by episodes of recurrent inflammation of superior cornea tarsal and bulbar conjunctiva, limbus Pupillary signs include Knies (uneven pupil dilatation in dim light), Loewis (dilation of pupil in 1/1000 adrenaline), Lowens (extensive hippus of consensual light reaction) Motility signs include Moebius (defective convergence)Sukers (inability to maintain fixation in extreme lateral gaze) ballets (paralysis of extraocular muscle) Wilders (jerky eyes on abduction to adducton) Globe signs include Means sign(increased scleral show on upgaze, Rosenbachs (tremor of gently closed eye) Snellen Donder (bruit over eye)Payne Trousseau (dislocation of globe) Reesman (bruit over lid) Lab investigations in TAO include thyroid hormone assays are done to detect overt or covert hypothyroidism. TSH is a useful screening test since it is very sensitive. A small change in serum t4 produce a many fold increase in TSH, hence subclinical disease detected earlier. It is less affected by nonthyroid disease; not affected by alterations in binding proteins. False positives are seen in patients on dopamine, steroids, first trimester of pregnancy, old age, hypopituitarism, hospitalization for psychiatric illness. Normal total T4 is 4.5-12.5microgram/dl and T3 is 80-200 ng/dl.. serum TSH is 0.3-5 mIu/ml, Hyperthyroidism<0.15 mIu/ml, hypothyroidism >5.7 mIu/ml

In addition to t3 and t4 assays, TRAbs, antithyroglobulin antibody, antomicrosomal antibody, anticolloidal immunoglobulin, antinuclear antibody may be done.

Imaging modalities include sonography, tomography and MRI.CT findings in a nutshell are enlarged muscle with tendon sparing,normal orbital fat, occasional slight bowing of medial wall-coca cola sign,optic nerve compression, rarely lacrimal gland involvement, absence of orbital masses and sinus involvement[13.]

B Scan USS demonstrate enlarged EOM as echo free area between orbital fat and bone, increased delineation of EOM margin, posterior scalloped or indented orbital fat,doubling of optic nerve sheath in optic neuropathy,no detectable neoplasm.

MRI provide better soft tissue spatial resolution and delineation of compressive optic neuropathy[14].

The following management measures are taken. For mild active cases, artificial tears, sunglasses, bed head elevation, selenium[15] (200 microgram/ day for 6/12). fresnel type prisms, botulinum toxin are given.

For mild inactive cases, artificial tears, prism, botulinum toxin, surgical mullerectomy, blepharoplasty are advocated. For moderate and severe ophthalmopathy, IV methyl prednisolone pulse therapy for a maximum 8g cumulative dose given. If unresponsive, immunosuppressants like cyclosporine. taclizumab or rituximab tried[16].

If muscular involvement is predominant, orbital radiotherapy is done.

For moderate to severe inactive cases cases primary orbital decompression, strabismus surgery, levator recession, blepharoplasty done.

CONCLUSION

The clinical profile of TAO shows the significance of various eye manifestations in terms of both signs and symptoms. It has gross cosmetic implications and significant visual morbidities too. Since no association of serum thyroid hormones has been established to the severity, extensive research on pathogenesis and predictive markers are yet to be established. The scenario of euthyroid and unilateral findings support this fact. A larger study including immunological markers may be required to predict appearance and severity of eye disease. This may help to monitor the treatment modalities and consequences better.

Sources of support: none

Abbreviations

TAO-Thyroid associated ophthalmopathy
EOM-Extraocular muscles.

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