Original Article

Ophthalmic Manifestations of Thyroid Orbitopathies

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ABSTRACT

OBJECTIVES: To describe age and sex specific rates of ocular/orbital involvement in thyrotoxic patients, to determine the rates of all components of NOSPECS classification system in patients with thyroid orbitopathies and to determine the relative magnitude of low and high index orbitopathies.

STUDY DESIGN: Prospective study.

METHODS AND MATERIALS: A total of 100 thyrotoxic patients of all age groups and both sexes were examined at the Department of Ophthalmology, JPMC, Karachi.

RESULTS: Male to female ratio was1:2.5. Age range was12-80years. Mean age was 36.59±13.81. The difference in age according to sex was found statistically non significant (P=0.60). Seventy-four percent patients had some sort of orbitopathy. Lid sign happened to be the most persistent sign of the orbitopathies (74%). The rates of the components of the NOSPECS classification system were N=26%, O=56%, P=16%, E=11%, C=13%, S=7% respectively. Patients with low index thyroid orbitopathy were 83% and 17% patients were with high index orbitopathy. High index orbitopathy was found to be more common in the males with age above 40 years.

CONCLUSION: The occurrence of thyroid orbitopathy appears to be independent of age and sex. Low index orbitopathies are more common than high index orbitopathies. Males are more at risk of developing high index orbitopathy than females.

KEY WORDS: Thyroid Orbitopathies, thyrotoxic, NOSPECS.

INTRODUCTION

Dysthyroid orbitopathy is an autoimmune disorder usually associated with Grave's disease [1, 2]. It is characterized by inflammation, edema and secondary fibrosis of the orbital tissues resulting in a variety of clinical manifestations. These include eyelid edema, eyelid retraction, conjunctival injection and chemosis, exposure keratopathy, proptosis, restrictive myopathy and compressive optic neuropathy. Other disorders like Hashmito's thyroiditis, thyroid carcinoma, primary hyperthyroidism and neck irradiation can have similar ocular manifestations[3]. Approximately 40% of patients with Grave's disease have or will develop thyroid orbitopathy. Subclinical alterations can, however, be seen on ultrasonography or computed tomography (CT) in almost all cases. Of these patients with thyroid orbitopathy approximately 80% are clinically hyperthyroid and 20% are clinically euthyroid[3]. Muhammad S et al[4] found 49% of thyrotoxic patients manifested with eye signs at Multan. Optic neuropathy, an uncommon manifestation occurs in 5% of patients with Grave's ophthalmopathy.[5] Therapies for non-sight-threatening disease range from supportive measures only to medical therapies for active eye disease and surgical rehabilitation for burnt-out disease. Intravenous steroids and orbital radiotherapy are the mainstays of medical therapy. Rehabilitative surgery is frequently a staged process that may involve sequentially: orbital decompression, strabismus surgery, and eyelid procedures[6]. The NOSPECS classification system was introduced by Werner in 1963 [7] so as to classify the various manifestations of thyroid orbitopathy which was latter on modified in 1989 by Bartalena and co-workers[8] in which the index scoring system was modified to place more significance on the vision-threatening manifestations of thyroid orbitopathy.

OBJECTIVES OF STUDY

The objectives of this study were to describe the age and sex specific rates of ocular/orbital involvement in thyrotoxic patients, to determine the rates of all the components of NOSPECS classification system in patients with thyroid orbitopathies, and to determine the relative magnitude of low and high index orbitopathies. "NOS" will be included in low index of severity, while "PECS" will be categorized as high index due to potential threat to vision.

PATIENTS AND METHODS

This study includes patients of all age groups and both sexes. All thyrotoxic patients presenting at the outpatients department of Ophthalmology and Atomic and Nuclear Sciences, JPMC Karachi, fulfilling the inclusion criteria described underneath were subjected to the planned ocular examination and investigations and were registered for study.

Study Design: Cross-sectional study

Sample Size: The annual OPD patients reported to Ophthalmology department for year 2004 were 50662. Expected proportion of thyroid orbitopathtic patients was 1.5%. Desired precision is taken as 5%. As such the sample size comes as 90 patients, it was rounded to one-hundred.

Study Settings: Department of Ophthalmology, JPMC, Karachi from 1st January 2005 to 31st December 2006.

METHODOLOGY

Patients who were diagnosed as thyrotoxicosis new as well as old cases. History of lid contractures resulting from trauma, chemical and thermal burns were excluded from the study. Similarly, patients having corneal ulcers opacities, glaucoma and orbital tumours were also excluded. A specific proforma (Data collection sheet) for the registered patients was established and a detailed history, ocular examination were carried out. Which included, visual acuity by Snellen's chart, color vision with Ischiara's chart, extraocular movements i.e. versions, ductions and vergences, lid movements to detect various lid signs associated with dysthyroid orbitopathy, slit lamp biomicroscopy of anterior segment to look for exposure keratitis, soft tissue involvement, superior limbic keratoconjunctivitis, intraocular pressure with applanation tonometer, direct and consensual pupillary light reflexes, direct and indirect ophthalmoscopy to look for fundus changes, and Exophthalmometry with Hertel's exophthalmometer. Automated visual field testing was performed when the examination was suggestive of the presence of optic nerve compression. Forced duction test was performed in cases showing restrictive myopathy. Blood complete picture and erythrocyte sedementation rate, blood sugar levels, thyroid function tests, thyroid scan, Computerized tomography (CT) scan whenever necessary were carried out. An ophthalmopathy index scorring system was adopted as that proposed by Bartlena and co-workers[6]. This allows quantitative evaluation of the severity of the ophthalmopathy with in each class of NOSPECS classification system.

STATISTICAL ANALYSIS

All the analysis and computation including the database development were done on the SPSS for Windows Ver. 10.0.

The comparison of mean values among different groups were done by using analysis of variance. The result were considered statistically significant if P value was less than or equal to 0.05.

The distribution of cases among various criteria were represented by their percentage. The difference in percentage was compared by the Chi-Square or Yates corrected Chi-Square test.

RESULTS

In this study total 100 patients of thyrotoxicosis were observed from 1st January, 2005 to 31st December 2006. seventy-two patients were females and 28 were male and male to female ratio was 1:2.5. The overall mean age was 36.59±13.81 years. Among females it was found to be 37.35±13.35 years and in males it was 34.72±14.93 years. The difference in age according to sex was not found to be statistically significant (P=0.60, t=0.86). It was observed that 77% of the cases fell between 21 to 50 years of age. Seventy-four out of 100 patients (74%) patients were found to have some sort of orbitopathy. Among them, 23 were males and 51 were females. Orbitopathy was found to be independent of sex when tested by Chi-square test (P=0.24, Chi-square=1.34) **(Table I)**.

NO PHYSICAL SIGNS OR SYMPTOMS (Class 0): No orbitopathy was found in 26 patients and this included 5 females and 21 males.

ONLY SIGNS (Class 1): Patients showing lid signs were assorted class 1 (O) in NOSPECS classification system. This rated 74/100 among thyrotoxic patients (Highest among various classes of NOSPECS (see **Table II**). Kocher's 41% Dalrymple's 47% von Graefe 39%, Rosenbock's 36% **(Table III)** so lid signs happened to be the most persistent sign of the orbitopathies, thus justifying the diagnostic criteria for Grave's orbitopathy as laid down by Bartley and Gorman[7]. Less common lid signs like Saintons which is delayed forehead wrinkling in upgaze and Jellenk's which is increased pigmentation of lids were recorded in the rate of 6% each **(Table III)**.

SOFT TISSUE INVOLVEMENT (Class 2): It is characterized by redness, watering, burning, and photophobia in the presence of conjunctival congestion, chemosis and lid puffiness. This was assigned the class-2 (S) of NOSPECS classification system. It was observed in 38 among thyrotoxic patients **(Table II)**. Risk of developing sight loss was less as compared to high index as Class-1 and 2 were included in the low index orbitopathy .

PROPTOSIS (Class 3): Hurtel's exopthalmometry of more than 20mm or difference of reading by 3mm was present in 16 patients. It was bilateral in 8 (8%) of the cases.

EXTRA-OCULAR MUSCLE INVOLVEMENT (Class 4): Restricted eye movements and positive forced duction test was seen in 11. Most of the patients showed restriction of elevation in this study. Differential IOP showing elevated pressures of more than

6mmHg in up gaze was seen in 11/100 (11%) patients.

CORNEAL INVOLVEMENT (Class 5): Exposure keratopathy of mild nature i.e. punctate epithelial erosions especially at inferior part of cornea was seen in 13 patients.

SIGHT LOSS (Class 6): Visual acuity, relative afferent pupil defect and defective colour perception were present in 7 patients. Signs of optic nerve compression i.e. swollen disc or disc pallor with visual field defect (central scotoma) was present in 7 patients. Proptosis, Extraocular muscle involvement (Myositis/muscle fibrosis), Corneal involvement (Exposure keratopathy) and Sight loss (optic nerve compression) were included in high index orbitopathy because of their potential for visual threat/problem. This was present in 17% of patients. Orbitopathy of low index was more oftenly seen in females as compared to males (90.3% in females verses 64.3% in males). Orbitopathy of high index was more oftenly seen in males as compared to females (35.7% in males versus 9.7% in females (M:F=58.8:42.2) and age groups was high than 30 years in both the sexes, most of the time **(Table I)**. The index of orbitopathy was found to be highly dependent on sex when tested by chi-square test (P=.003, chi-square=8.60).

Age and sex specific distribution of thyroid orbitopathies **(Table IV)** description was as follows:

Ten to twenty (10-20) years age group included 12 patients. All the patients were showing low index of orbitopathy (M:F.1:3).

Twenty-one to thirty (21-30) years age group included 25 patients, 15 patients were female and 10 patients were male. All female were showing low index of orbitopathy while in male 8 patients were of low index and 2 patients were of high index orbitopathy.

Thirty one to forty (31-40) years included 27 patients. Out of 27 patients 21 patients were females and 6 were males so male to female ratio was 1:3.5. Low to High index orbitopathy ratio was 4.4:1

Forty one to fifty (41-50) years included 25 patients. Male to female ratio was 1:5.2. Low index orbitopathy was present in one male and 18 females. High index orbitopathy was present in 3 males and 3 females.

Fifty to sixty years age group male to female ratio was M:F=3:4. Out of 3 male patients one was high index orbitopathy and two patients were of low index orbitopathy. In females out of 4, only 1 was of high index orbitopathy. Sixty and above age group included two males and two females. Both the males were showing high index orbitopathy while both the females were showing low index orbitopathy . Complete constellation of disease was seen in 7/100 patients with 95% confidence interval 1.0-21.4%.

TABLE I:
RATE AND INDEX OF ORBITOPATHY

	Males	Females	Total	
Orbitopathy Rate				
Orbitopathy	23(82%)	51(71%)	74(74%)	P-0.24 X^2=1.34
No Orbitopathy	5(18%)	21(29%)	26(26%)	
Orbitopathy Index				
High	10	7	17	P=0.003 X^2=8.6
Low	18	65	83	

TABLE II:
RATES OF COMPONENTS OF NOSPECS

Components of Nospecs	Observed Rates	95% Confidence Interval
N	26 (26%)	11.7 - 44.9
O	56 (56%)	36.7 - 74.0
S	38 (38%)	20.9 - 57.4
P	16 (16%)	5.3 - 33.4
E	11 (11%)	2.6 - 27.0
C	13 (13%)	3.6 - 29.7
S	7 (7%)	1.0 - 21.4

TABLE III:
RELATIVE PERCENTAGES OF LID SIGNS IN THYROTOXICOSIS

	No. of Patients	95% Confidence Interval
Dalrymple	47 (47%)	28.5 - 66.1
Kocher	41 (41%)	23.41 - 60.4
Von Graefe	39 (39%)	21.7 - 58.4
Boston	9 (9%)	1.8 – 24.3
Mean	13 (13%)	3.6 – 29.3
Rosenbach	36 (36%)	19.3 - 55.4
Griffith	9 (9%)	1.8 – 24.3
Stellwag	22 (22%)	9.0 – 40.5
Joffroy	18 (18%)	6.5 – 35.84
Sainton	6 (6%)	0.7 – 19.9
Gifford	23 (23%)	9.7 – 41.6
Jellonk's	6 (6%)	0.7 – 19.9
Grove	19 (19%)	7.1 – 37.0

TABLE IV:

AGE AND SEX DISTRIBUTION OF ORBITOPATHIES IN THYROTOXIC PATIENTS

Age Group	Males		Females		LI0 with in age group	HI0 with in age group
	LI0	HI0	LI0	HI0		
Upto 20	3	0	9	0	12/12	0/12
21-30	8	2	15	0	23/25	0/25
31-40	4	2	18	3	22/27	5/27
40-50	0	4	19	2	19/25	6/25
51-60	2	1	3	1	5/7	2/7
>60	0	2	2	0	2/4	2/4
Total	**17**	**11**	**66**	**6**	**83/100**	**17/100**

DISCUSSION

Orbitopathy rate was 74% in this study and this is different from other study, which show rates as high as 91.4% [10]. Orbitopathy rates in Graves' disease were strangely low in the study of Carter who reported it to be 2% to 7%[11] Sex distribution in patients showing orbitopathy female to male ratio is 2.5:1 which is close to other studies[10]. While in another study done by Wiersinga and associates[12] in 1989 female to male ratio of Graves' orbitopathy patients was about 3:1. In the study of Bartley, the female to male ratio was 6:1 [13]. In the study of Marcocci-C and associates published in April 1989 it was 3.4:1[10]. Age distribution was showing highest rate in 21-30 years (25%), 31-40 years (27%), 41-50 years (25%) age groups in our study. It was 5th decade in the Marcocci and Bartlena study[10]. Age range covering the maximum cases was 21-50 years (77%). The orbitopathy rate in 30-50 years age group in our study remained about 4:1 for females and males and is thus comparable to other studies [13]. The occurrence of orbitopathy was independent of sex when tested by chi-square test. Kendler and his associates have also reported no significant difference in orbitopathy rates between males and females [14]. Lid retraction was the most common orbitopathy and occurred in 74% of the thyrotoxic patients. Bartley also published the same sign to be the most persistent[13]. Kocher's, Dalrymple's and von-Graefe's were the most frequent seen signs and were present in more than 30% of the thyrotoxic patients at the time of examination. 55% is reported in Bartley's study [13]. Unilateral or bilateral proptosis 20mm or more by Hertel's exophthalmometer was seen in 16 thyrotoxic patients (16%). Bartley reported an extremely high rate (60%) which was not seen in our study [11]. High index orbitopathy was more common among males 10/17 (58.8%) as compared to females 7/17 (42.2%) and commonly involves relatively higher age group i.e. above 40 years and this is comparable to the results of Perros and colleagues [15]. Differential IOP rising more than 6mmHg in upgaze was seen in 11 out of 100 thyrotoxic patients, a rate of 11%. It was positive in the patients showing restricted myopathy. The rate reported by Bartely was very high i.e. 40% [13]. Signs of optic nerve compression were present in 7 out of 100 patients (7%), and this is comparable to other studies i.e. 9.9% in the study of Perros and his associated published in April 1993[12] and 6% in the study of Bartely-GB [13]. In a retrospective study of 89 patients with Grave's disease done by Barth-A and colleagues,[16] class 1 or greater was found in 34%, proptosis more than 20mm in 8% and severe ophthalmopathy i.e. class 4 to 6, in 7% of the patients before treatment with radioiodine and 2 to 5% as reported by Domend-M and colleagues[17]. In comparison to the above mentioned study, this study shows class 1 or greater was found in 56%, proptosis of more than 20mm was found in 16%, which is quite different. Severe ophthalmopathy was found in 7% which is same to the study done by Barth and his colleagues.[16]

CONCLUSION

The occurrence of thyroid orbitopathy appears to be independent of age and sex. Low index orbitopathy is more common than high index orbitopathy. Males are more at risk of developing orbitopathy than females.

RECOMMENDATIONS:

It is recommended that multicentric studies, hospital and community based, may be carried out to

A. Identify risk factors for:

i. Development of thyrotoxicosis;
ii. Development of low index orbitopathy;
iii. Development of high index orbitopathy;

B. Identify early waring signs.

C. Measures to prevent this sight threatening condition.

ACKNOWLEDGEMENT

These data were possible to be collected by cooperation of Dr.Akhter Memon (Consultant nuclear physician Radio-isotope Centre, J.P.M.C Karachi) and Tariq M. Aziz (Associate Professor and Head of Ophthalmology Department, Jinnah Postgraduate Medical Centre, Karachi).

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