

OPHTHALMIC MANIFESTATION OF GRAVES' DISEASE

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ABSTRACT

Objective: The purpose of this study is to find out various ophthalmic sign in patients with Graves' disease, their relative frequency and the percentage of patients severely affected resulting in loss of vision.

Material and Methods: This prospective study is based on finding ophthalmic signs in one hundred patients with established Graves' disease attending ophthalmic and medical units of Khyber Teaching Hospital Peshawar as well as Institute of Radiotherapy and Nuclear Medicine (IRNUM) Peshawar. The total duration of study is seventeen months i.e. from August 1994 to December 1995. For study, a proforma has been set up giving all the possible ophthalmic signs which may be present in patients with Graves' disease. Patient's name, age, sex and address were recorded. The proforma also gives information about the mode of presentation that how and when the patients with Graves' disease seek medical advice.

The age-sex distribution of Graves' disease and the percentage of patients with positive family history and smoking history are also sorted out. Relation of thyroid hormone level to severity of ophthalmic signs and percentage of euthyroid patients with ophthalmopathy is also taken into consideration. Moreover unilateral and bilateral presentation is also compared.

Results: A total of one hundred patients with Graves' disease were examined, over a period of seventeen months. These patients were examined thoroughly for possible ophthalmic signs. Eighty four patients were female and 16 patients were male. Family history was positive in 32 percent of patients. Association between smoking habit and ophthalmopathy could not be established. Their mean age was 45 years (age range 15-60 years). Usually the patients with Graves' disease sought medical advice within two years after developing symptoms. Fifty eight patients showed ophthalmopathy ranging from mild to moderate form with no case with severe ophthalmopathy. About 71 percent patients showing ophthalmopathy

were hyperthyroid. The common ophthalmic signs were lid retraction, lid lag, exophthalmos and mild conjunctival congestion and chemosis. No case of extraocular muscle motility defect or optic nerve compression was found in this series of patients. Infiltrative dermatopathy, being a rare finding, was not observed in this study.

Conclusion: Ophthalmopathy occur in about 50% of patients therefore ophthalmologist has an important roll in the diagnosis and management of this disease. These patients can be made comfortable by local and systemic therapy, radiation or surgical intervention while waiting for spontaneous remission of the disease process as none of these therapies can alter the natural course of Graves' ophthalmopathy. After stabilization of disease strabismus surgery followed by lid surgery can correct diplopia and improve cosmesis.

Key words: Graves' disease, Graves' Ophthalmopathy, Thyroid related orbitopathy.

INTRODUCTION

Graves' disease is a multisystem autoimmune disorder characterized by diffuse goitre, thyrotoxicosis, infiltrative ophthalmopathy, lymphadenopathy, infiltrative dermatopathy and presence in the blood of thyroid stimulating immunoglobulins.

It is a classical example of a disorder in which cooperation between ophthalmologist and internist results in a rewarding and more comprehensive approach to patient's care. "The term Graves' ophthalmopathy refers to a patient with orbital inflammation but the most preferred term nowadays is thyroid related orbitopathy (TRO)¹.

In 12th century syeed Ismail Al-Jurjani described a relationship of exophthalmos with goitre, however "modern association of hyperthyroidism, diffuse goitre and exophthalmos has been attributed to work of Caleb Hillier Parry, Robert James Graves and Carl Von Basedow"². Various theories have been put forward to explain the pathogenesis of Graves' disease and Graves' ophthalmopathy. The most commonly accepted are abnor-

mality in hypothalamo-pituitary axis and autoimmunity.

Abnormality in hypothalamopituitary axis can be explained on the basis of finding exophthalmos producing substance (EPS) in patient's serum and "finding of low affinity TSH receptor in the retrobulbar fat cells"³ the stimulation of which can cause infiltration and edema of retrobulbar fat.

According to autoimmune theory it may be humoral or cell mediated immunity. Humoral immunity can be explained on the basis of finding LATS, LATS-protector, IgE, IgA, antithyroglobulin and antimicrosomal antibodies but these have no direct relation with severity of ophthalmopathy, however "reduction in antimicrosomal antibodies in euthyroid Graves' ophthalmopathy indicate some immunologic remission"⁴.

Cell mediated immunity is thought to play an important role in pathogenesis of Graves' ophthalmopathy, in which T-lymphocytes are activated by CD (cluster designation) molecules and these activated T-cells secrete cytokines which cause proliferation of fibroblast and increased gly-

cosaminoglycans synthesis by these fibroblasts to produce ophthalmopathy. Histological finding of mononuclear cell infiltration and presence of cytokines in the orbital tissue favours this hypothesis.⁵ The most commonly found 64 KDa protein co-expressed both in thyroid and orbit favours strong association between Graves' disease and ophthalmopathy³⁻⁶. Various ophthalmic signs, ranging from mild to severe, are frequently associated with Graves' disease which can develop before, during or after the development of general signs and symptoms of Graves' disease. The eye signs of Graves' disease depend upon the local enlargement of orbital tissue, excluding the globe. The eye signs of Graves' disease consists of eyelid retraction, lid lag, lid edema, conjunctival congestion and chemosis, exophthalmos, extra ocular muscle involvement and optic nerve involvement.

The purpose of this study was to find out various ophthalmic sign in patients with Graves' disease, their relative frequency and the percentage of patients severely affected resulting in loss of vision. The age-sex distribution of Graves' disease and the percentage of patients with positive family history and smoking have also been looked into. Relation of thyroid hormone level to severity of ophthalmic signs and percentage of euthyroid patients with ophthalmopathy is also taken into consideration. Moreover unilateral and bilateral presentation is also compared.

MATERIAL AND METHODS

This study is based on finding ophthalmic signs in one hundred patients with established Graves' disease attending ophthalmic and medical unit as well as Institute of Radiotherapy and Nuclear Medicine (IRNUM) Peshawar. The total duration of study is seventeen months i.e. from August 1994 to December 1995. In this study, it was

noted that about 70 percent of patients with Graves' disease attend IRNUM for their complaints. It is due to the reason that almost all the laboratory investigation for thyroid functions are done in IRNUM. Moreover, IRNUM offers these patients free treatment by radio active iodine (I^{131}). As these patients usually present to other disciplines for their complaints, cooperation of other colleagues helps a lot to sort out established cases of Graves' disease.

To conduct this study, a proforma had been set up giving all the possible ophthalmic signs which may be present in patients with Graves' disease. Patient's name, age, sex and address were recorded. The proforma also gives information about the mode of presentation that how and when the patient with Graves' disease seek medical advice.

The diagnosis of Graves' disease was established on the basis of present history, past history and family history of hyperthyroidism. History of any therapy like anti-thyroid drug, radioactive iodine or surgery was also noted. History of smoking and other autoimmune disorders, like diabetes and rheumatoid arthritis was also recorded. Patient's pulse rate and blood pressure were taken routinely.

Investigations, like serum triiodothyronine, serum thyroxine, serum thyroid stimulating hormone and thyroid scan were done and records of the previous results was also considered.

Ultrasonography of eight patients and C.T. Scan of three patients was done. All these patients showed increase in soft tissue mass and enlargement of extraocular muscles. Ultrasonography and C.T. Scan of all patients with ophthalmopathy could not be done because of poor socioeconomic state and poor compliance of the patients.

The patient's eyes were examined thoroughly for all possible ophthalmic signs.

Visual acuity was recorded with and without glasses. Any defect in colour vision and visual field was noted. Exophthalmometry was done with Hertel exophthalmometer. Strabismus, diplopia, abnormal head posture and limitation of ocular movement either paretic or fibrotic were noted.

Eyelids were examined for any pigmentation, swelling, retraction, lid lag, fine tremor, infrequent blinking and lagophthalmos. Slit lamp examination of anterior segment was done to see conjunctival congestion and chemosis, exposure keratitis, superior limbic keratoconjunctivitis, pupil reaction and uveitis. Fundus examination was done for any vein engorgement, disc swelling, optic atrophy and coloridal folds. Intra ocular pressure was recorded in primary and upgaze positions.

RESULTS

A total number of one hundred patients with Graves' disease were examined, of which eighty four patients were females and sixteen patients were males with a female : male ratio of 5.25 : 1 (Table 1). Out of total hundred patients, 79 (79 percent) patients presented in fourth and fifth decade of their life. 64 (76 percent) females and 15 (94 percent) males presented in fourth and fifth decade of their life.

Family history was positive in 32 percent of patients, six (37.5 percent) males gave positive family history while 26 (23.96 percent) females gave positive family history. No patients gave history of smoking

and diabetes. One female gave history of joints pains.

In this study, it was also seen that 50 percent of patients usually seek medical advice usually early within two years after developing symptoms of Graves' disease (Table 2).

It was observed that 42 patients with Graves' disease did not develop ophthalmic signs of which 36 patients were female and 6 patients were male.

Among the patients showing ophthalmopathy 29:31 percent patients were euthyroid and 70.69 percent were hyperthyroid. (Table 3)

We have divided ophthalmopathy broadly in to Non-infiltrative ophthalmopathy and infiltrative ophthalmopathy. Non infiltrative ophthalmopathy include only lid retraction with or without lid lag caused by hyperaction of Muller's muscle and levator palpebrae superioris muscle. It does not include the lid retraction caused by actual disease process involving the muscle (Table 4).

Infiltrative ophthalmopathy include soft tissue involvement, exophthalmos and extraocular muscle involvement. Corneal exposure and optic nerve compression occur when infiltrative ophthalmopathy become severe (Table 4).

Sex distribution of Graves' ophthalmopathy is shown in Table 5. Out of total 58 patients with ophthalmopathy 10 patients were male and 48 patients were females.

AGE / SEX DISTRIBUTION OF GRAVES' DISEASE (100 PATIENTS)

	15-19 Years	20-29 Years	30-39 Years	40-49 Years	50-59 Years	Total
MALE	1	0	7	8	0	16
FEMALE	1	14	30	34	5	84
TOTAL	2	14	37	42	5	100

TABLE 1

DURATION OF THE DISEASE AT THE FIRST PRESENTATION OF PATIENTS (100 PATIENTS)

	Male	Female	Total
6 month-3 yrs	10	40	50
3-6 yrs	0	22	22
6-11 yrs	5	12	17
12-20 yrs	1	10	11
Total	16	84	100

TABLE 2

Further detail and relative frequency of ophthalmic signs are shown in Table 7. The commonest signs of Graves' ophthalmopathy noted in this study was lid retraction, (fig 1) including both non infiltrative and infiltrative type. Lid lag (fig. 2) was present in 16 (27.59 percent) patients. Bilateral exophthalmos (fig. 3) was present in 5 (31.25 percent) male patients and 8 (50 percent) female patients (table 6). Other ophthalmic signs were skin pigmentation of lid, fine tremor of closed lids, lagophthalmos, Mobius signs (imperfect convergence) puffy eyelids (fig. 4), conjunctival congestion, conjunctival chemosis, superior limbic keratoconjunctivitis and exposure keratitis.

Fundus examination showed engorged veins in 9 patients (15.52 percent) and choroidal folds 2 patients (3.45 percent). Raised intraocular pressure was noted in 6 patients. No patient with diplopia, extraocular muscle motility defect and optic nerve involvement was seen.

THYROID STATUS OF PATIENTS WITH OPTHALMOPATHY (58 PATIENTS)

	Euthyroid	Hyperthyroid	Total
Male	3(5.17%)	7(12.06%)	10
Female	14(24.14%)	34(58.62%)	48
Total	17(29.31%)	41(70.69%)	58

TABLE 3

AGE DISTRIBUTION OF GRAVES' OPTHALMOPATHY (58 PATIENTS)

	Non infiltrative	Infiltrative ophth.	Total
15-19 yrs	0(0%)	2(3.45%)	2
20-29 yrs	2(3.45%)	5(8.62%)	7
30-39 yrs	12(20.69%)	12(20.69%)	24
40-49 yrs	11(18.96%)	14(24.14%)	25
50-59 yrs	0	0	0
Total	25(43.10%)	33(56.90%)	58

TABLE 4

DISCUSSION

Graves' disease is a systemic autoimmune disorder characterized by a genetic predisposition, an increased incidence in young women, the presence of thyroid stimulating immunoglobulins and an uncertain etiology "It is more prevalent in iodine rich area than in iodine deficient area"¹⁷. The frequent association of Graves' disease and ophthalmopathy favours an autoantigen co-expressed in thyroid and orbit but still a definite antigen could not be found. The most frequently identified antigen co-expressed in thyroid and retrobulbar tissue is a protein of 64 KDa molecular weight.³⁻⁶

Various theories like abnormality in hypothalamopituitary axis^{3,22}, humoral immunity^{2,4,24} and cell mediated immunity^{2,23} have been put forward to explain the pathogenesis of Graves' disease and its associated ophthalmopathy. The basis for diagnosis of

SEX DISTRIBUTION OF GRAVES' OPTHALMOPATHY (58 PATIENTS)

Sex	Non infiltrative	Infiltrative ophth.	Total
Male	2(3.45%)	8(13.79%)	10
Female	23(39.66%)	25(43.10%)	48
Total	25(43.10%)	33(56.90%)	58

TABLE 5

EXOPHTHALMOS UNILATERAL VERSUS BILATERAL PRESENTATION (16 PATIENTS)

	Unilateral	Bilateral	Total
Male	1(6.25%)	5(31.25%)	6
Female	2(12.5%)	8(50%)	10
Total	3(18.75%)	13(81.25%)	16

TABLE 6

Graves' disease is clinical and chemical hyperthyroidism, past history and family history of hyperthyroidism. In euthyroid Graves' disease routine thyroid function tests are normal but more sophisticated tests

RELATIVE FREQUENCY OF OPTHALMIC SIGNS IN GRAVES' OPTHALMOPATHY (58 PATIENTS)

Ophthalmic sign	Female	Male	Total	%age
Skin pigmentation	1	1	2	3.45
Darlymple sign	38	6	44	75.86
Lid retraction	22	3	25	43.10
Von graefe sign	13	3	16	27.59
Fine tremor of closed lids	11	2	13	22.41
Lagophthalmos	3	2	5	8.62
Exophthalmos	10	6	16	27.59
Mobius sign	3	3	6	10.34
Puffy eyelids	22	7	29	50
Conjunctival congestion	25	8	33	56.90
Conjunctival Chemosis	17	5	22	37.93
Superior limbic	3	0	3	5.17
K-Conjunctivitis				
Exposure keratitis	3	2	5	8.62
Engorged veins	5	4	9	15.52
Choroidal folds	1	1	2	3.45
Raised intraocular pressure	4	2	6	10.34

TABLE 7



Fig. 1. Lid Retraction

like, free T3 and T4, T3 suppression test, TRH stimulation test and presence of thyroid stimulating immunoglobulin can help in the diagnosis.

In this study 32 percent of patients showed positive family history suggesting a possible role of genetic factor in its pathogenesis. In another study 20 percent positive family history has been reported¹⁸. Females are affected more (84 percent of total patient) usually in the 4th and 5th decade of life. The female to male ratio in this study was found to be 5.21 : 1 which is not much different from other reports⁹. In this study it was found that 50 percent of patients seeked medical advice with in two years after developing symptoms of Graves' disease.

Although association between cigarette smoking and Graves' ophthalmopathy has been reported^(10,11,12) but in this study we could not find any association between



Fig. 2. Lid Lag.



Fig. 3. Bilateral Exophthalmos.

cigarette smoking and Graves' ophthalmopathy. Moreover most of our patients were female and in our society female usually do not smoke. In another study recently done, no correlation was found between ocular changes and history of smoking in Graves' disease¹³.

In Graves' disease, ophthalmopathy occur in about 50 percent of patients. In this study 58 patients showed some form of ophthalmopathy ranging from mild to moderate ophthalmopathy. Total male patients were 16, among which 10 patients (62.5 percent) developed ophthalmopathy and total female patients were 84 among which 48 patients (57 percent) developed ophthalmopathy. In another report sixty six percent patients with Graves' disease developed ophthalmopathy with in eighteen months of



Fig. 4. Bilateral Puffy Eye Lids showing soft tissue involvement.

diagnosis with no significant difference between males and females¹⁴. However as low as 20 percent incidence of ophthalmopathy has been reported in Graves' disease¹⁵.

In this study patients showing ophthalmopathy, 70.69 percent were hyperthyroid and 29.31 percent patients were euthyroid. In other studies hyperthyroid patients with Graves' ophthalmopathy ranged from 61 percent to 64 percent^(15,16).

In this study the peak incidence of Graves' ophthalmopathy was seen between 40 and 50 years of age. In another report "Bimodal peak incidence has been found in both females and males, the peak incidence for female being 40 to 44 years and 60 to 64 years and for males 45 to 49 year and 65 to 69 years¹⁷. As in our study the maximum age of patient is sixty years, the second peak incidence of Graves' ophthalmopathy was not observed.

In females non-infiltrative and infiltrative ophthalmopathy occurred nearly equally, 47.92 percent and 52.08 percent respectively. In males the incidence of infiltrative ophthalmopathy was more, being 80 percent while non infiltrative ophthalmopathy was present only in 20 percent of male patients.

Graves ophthalmopathy consists of lid retraction, lid lag, lid edema, exophthalmos, soft tissue changes, extraocular muscle involvement, corneal exposure and optic nerve compression. However lid retraction, lid lag and exophthalmos are the usual diagnostic feature of Graves' ophthalmopathy¹⁸.

Graves' disease affect levator muscle and extraocular muscle differently, the levator muscle become hyperactive causing lid retraction whereas the extraocular muscle become fibrotic and restrict the motion of eyeball¹⁹. Lid retraction was the most common finding, present in 75.86 percent of patients, lid lag was found in 27.59 percent patients. Mild conjunctival congestion was

seen in 56.90 percent and conjunctival chemosis in 37.93 percent of patients. Exophthalmos was found in 27.59 percent of patients, ranging from mild to moderate degree. Exophthalmos was axial and 81.25 percent patients had bilateral exophthalmos. Lid pigmentation was a rare sign present in 3.45 percent of patient. In another study 5 percent patient showed lid pigmentation⁸.

Lagophthalmos was present in 5 patients (8.62 percent) and all developed exposure keratitis of inferior third of cornea. Other less commonly found ophthalmic signs were imperfect convergence 6 patients (10.34 percent), superior limbic keratoconjunctivitis 3 patients (5.17 percent) engorged veins 9 patients (15.52 percent), choroidal folds 2 patients (3.45 percent) and raised intraocular pressure 6 patients (10.34 percent). Increase in intraocular pressure was found upto 22 mm of mercury on upgaze. Increase in intraocular pressures on upgaze is a normal finding augmented by Graves' infiltrative ophthalmopathy²⁰.

No case of extraocular motility defect and optic nerve compression was found in this study. Infiltrative dermatopathy is a rare phenomena and no case of pretibial myxedema and clubbing of finger has been noted, similar to the results of another study¹⁵. It has been reported that dysthyroidism is associated with more severe Graves' ophthalmopathy and therefore meticulous control of thyroid function is very important in the management of Graves' ophthalmopathy²¹. In this study, also abnormal thyroid function tests were found to be related to severity of eye symptoms.

Various types of treatment are available to decrease the severity of ophthalmic signs but non of them can alter the natural course of the disease. However one can help these patients to be more comfortable with these therapies while waiting for spontaneous remission of disease.

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