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Factors associated with severity of orbitopathy in patients with Graves' disease

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Abstract:

PURPOSE: Graves' orbitopathy (GO) is one of the most frequent orbital disorders and is the most common cause of proptosis in adults. GO is described as chronic inflammation of orbital and periorbital tissues. This study aimed to evaluate the risk factors for severe GO in patients with Graves' disease (GD).

MATERIALS AND METHODS: This was a prospective cross-sectional study done on 52 newly diagnosed patients of GD with GO documented by thyroid ^{99m}Technetium-pertechnetate scan at our center between May 2016 and May 2019. All patients underwent a comprehensive ophthalmological examination and laboratory and hormonal analysis. Clinical Activity Score (CAS) and severity were estimated as per the European Group on Graves Orbitopathy. Thirty-four patients with mild GO were compared with 18 patients with moderate-to-severe GO (severe) for baseline risk parameters.

RESULTS: Majority of the patients had mild orbitopathy (34 [65.4%]) followed by moderate to severe (18 [34.6%]). CAS was active in 13.5% of the study group. There was a statistically significant male preponderance in severe GO. Current smoking increased the risk of severe GO (P = 0.003). Duration of GD symptoms at presentation was statistically significantly longer in severe GO patients than mild GO (P = 0.004). Thyrotropin receptor antibody (TRAb) titer significantly increased in severe GO group (6.2 ± 2.4 IU/L) when compared to mild GO (3.2 ± 1.6 IU/L) (P < 0.001). TRAb positivity was similar between groups. Braley's sign, i.e., the differential intraocular pressure (IOP) of >6 mmHg, was statistically significantly higher in severe GO (P < 0.001). Male gender, current smoking, TRAb >2 upper limit of normal (ULN), and differential IOP >6 mmHg were found to be associated with severe GO.

CONCLUSION: Approximately 35% of the patients with GO have severe disease, with a higher risk in men. This study identified male gender, current smoking, TRAb >2 ULN, and differential IOP >6 mmHg to be associated with severe GO.

Keywords:

Clinical Activity Score, Graves' disease, Graves' orbitopathy, severe orbitopathy, thyrotropin receptor antibody

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Introduction

Graves' disease (GD) is the most common cause of hyperthyroidism, whereas Graves' orbitopathy (GO) is the most frequent orbital disorder and is the most common cause of unilateral and bilateral proptosis in adults.[1-3] It most likely involves an antibody reaction against the thyroid-stimulating hormone receptor (TSHR) that results in the activation of T cells against tissues in the retro-orbital space that share antigenic epitopes with thyroid follicular cells.[4,5] GO is due to autoimmune pathogenesis with important genetic and environmental influences, particularly smoking.[6] The risk of GO is found to be related to active smoking and is proportional to the number of cigarettes smoked per day. Among the risk factors predisposing to GO, smoking, older age, radioactive iodine, stress, trauma,

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and thyroid dysfunction appear to correlate with the onset of GO; the reasons underlying these predisposing factors remain unclear.[7-10]

The importance of the role of insulin-like growth factor 1 (IGF-1) receptor as a retro-orbital antigen and the role of serum IGF-1 and IGF-1 receptor antibodies acting synergistically with TSHR antibodies are well known.[11,12] IGF-1 and its receptor may represent an important switch, regulating the quality and amplitude of immune responses.[6,13] These immune processes lead to an active phase of inflammation, with lymphocyte infiltration of the orbital tissue and release of cytokines that stimulate orbital fibroblasts to multiply and produce mucopolysaccharides (glycosaminoglycans), which absorb water. In consequence, the extraocular muscles thicken and the adipose and connective tissues of the retro-orbit increase in volume.[6,13] Other risk factors previously studied included genetic polymorphisms of the thyrotropin receptor. At present, genetic testing is not yet warranted as none of the polymorphisms impart a high enough risk of GO.[10] Thyrotropin receptor antibody (TRAb) may be useful in predicting the course of GD and response to therapy, but it is unknown if they are predictive of GO development.[10]

GO is clinically evident in about a third of patients with GD, although it can be demonstrated by orbital imaging in nearly all.[6,13,14] Most patients have a mild eye disease, while approximately 5% have severe potentially sight-threatening ophthalmopathy.[6] GO is usually bilateral (90%), asymmetrical in 10%–15%, and unilateral in 2% of cases.[15,16] A more detailed protocol with a soft-tissue atlas was published[17] and adopted by the European Group on Graves' Ophthalmopathy (EUGOGO);[18] however, a further less detailed protocol has also been published from North America,[19] and a worldwide consensus remains elusive. Given the variable presentation of GO, summary descriptions are of little use, and each feature should be assessed individually.

Patients most commonly present in the third to fifth decades of life, with women more commonly affected, with a female-to-male ratio of 2–3:1 for GO.[20] Ethnicity is likely to play an important role in the development of GO.[10,21,22] A study on patients with GD revealed that Europeans have a higher risk of GO compared to Indians.[21] The presentation of GO also varies in different ethnic groups. GO may precede or follow endocrinologic manifestations, however they typically present within 18 months of each other.[4] GO occurred before the GD in 23%, concurrent with GD in 39%, and after GD in 37%.[20] We designed a study to determine the risk factors predisposing patients to severe orbitopathy in patients with GD.

Methods

It was a single-center, prospective, cross-sectional study conducted on adult patients with GD with GO. This study was carried out in the Department of Endocrinology and Ophthalmology of GMC Srinagar, Kashmir. The study was conducted in accordance with the ethical standards stated in the Declaration of Helsinki. The study was approved by the institutional ethical committee (GMC Srinagar).

Study subjects

A total of 52 consecutive patients with diagnoses of GD with GO, who fulfilled the eligibility criteria, were recruited in the study. This study was conducted over a period of 3 years from May 2016 to May 2019. Information regarding various demographic characteristics was taken through well-structured questionnaires from all participants. Besides a detailed history, physical examination and laboratory and biochemical workup were carried out. Informed consent was obtained from all the recruited participants.

Eligibility criteria

Inclusion criteria included patients aged >18 years with GD. The diagnosis of GD was made based on the clinical features of thyrotoxicosis, elevated thyroid hormones, suppressed thyrotropin (thyroid-stimulating hormone), and thyroid ^{99m}Technetium-pertechnetate scan evidence of diffuse homogeneous increased uptake in both lobes of the thyroid. The diagnosis of GO was based on the criteria of Bartley and Gorman. Exclusion criteria included (i) GD without GO and (ii) orbitopathy other than GD.

Detailed study design

In each patient, the initial screening for GO was performed by an endocrinologist. The patients were referred to the department of ophthalmology. Ophthalmological measurements included the following: visual acuity, pupil response and color vision, Inflammatory Index Score, extraocular movement and strabismus, lid measurements including palpebral aperture, marginal reflex distance, lid retraction, and Hertel's exophthalmometry. The findings were classified as per the EUGOGO[23] recommendations-preliminary case record form. The diagnosis of GO was based on the criteria of Bartley and Gorman.[24] The clinical activity of GO was classified as per the Clinical Activity Score (CAS) recommended by the EUGOGO. A CAS of < 3 is considered inactive and ≥ 3 as active GO. The severity of GO was classified into mild, moderate to severe (severe), and sight threatening (very severe) based on the EUGOGO classification. Severity was based on one or more of the following: lid retraction, soft-tissue involvement, degree of proptosis, presence of diplopia, corneal exposure, and optic nerve involvement. The degree of proptosis was measured

using a Hertel's exophthalmometer. The normal value is <17 mm for males and <15 mm in females for Indians. A measurement of ≥20 mm was diagnosed as severe exophthalmos. The above cutoff has been previously validated in healthy North Indian population.[25,26] All patients who had clinical evidence of severe orbitopathy underwent computed tomography scan of the orbits. Serum total T3, total T4, and TSH were estimated by chemiluminescence immunoassay. Serum thyroid peroxidase antibodies (TPOAbs) were measured using radioimmunoassay. A cutoff value of TPOAb ≥20 IU/ml was considered positive with an analytical sensitivity of 2 IU/ml. Serum TRAb concentrations were determined with a second-generation enzyme immunoassay. A value of TRAb ≥1.5 IU/L was considered positive. The analytical sensitivity of the assay was 0.5 IU/l. Normal absolute neutrophil count (ANC) ranges from 1.5 to 8.0/mm^3. Neutropenia was defined as ANC <1500/µl.

Statistical analysis

Frequency distribution was assessed in terms of means ± standard deviation for quantitative variables and number (percentages) for categorical variables. The Student's *t*-test or Mann–Whitney U-test was used for the comparison of continuous variables as appropriate. The Chi-square test was used to compare categorical variables. Multivariate binary logistic regression analysis was performed to study the severity of GO (dependent variable) with various risk factors including duration of GD (months), gender, current smoking (in males only), CAS ≥ 3, TRAb titer, and differential intraocular pressure (IOP) >6 mmHg. P <0.05 was considered statistically significant. All the analyses were performed by the Statistical Package for Social Sciences version 21.0, (SPSS, Chicago, IL, USA).

Results

A total of 52 patients who met the inclusion criteria were included in the study. All the patients were of Kashmiri ethnicity. Table 1 shows the activity and severity of GO. The disease was of mild in severity in majority number of the patients (34 [65.4%]) and moderate to severe in 18 (34.6%) patients. None of the patients had any evidence of sight-threatening disease. Almost half of the study group (51.9%) had proptosis of > 20 mm. CAS was active in 13.5% of the study group.

Table 2 shows the baseline characteristics of GO divided on the basis of severity of orbitopathy (severe GO [n = 18] and mild GO [n = 34] groups). Demographic, clinical, and biochemical and laboratory parameters were compared between the two groups. The mean age of the patients with GO was 42.4 ± 10.2 years as compared to 39.5 ± 11.0 years (P = 0.358). There was a statistically significant male preponderance in severe GO group (P < 0.001). Current smoking increased the risk of severe GO (P = 0.003). Duration of GD symptoms at presentation was statistically significantly longer in severe GO patients than mild

Table 1: Activity and severity of Graves' orbitopathy as per the European Group on Graves Orbitopathy criteria

Characteristics	Number of patients (%)
Activity	
CAS ≥3	7 (13.5)
CAS <3	45 (86.5)
Severity	
Mild	34 (65.4)
Moderate to severe	18 (34.6)
Sight threatening	0

CAS=Clinical Activity Score

Table 2: Baseline characteristics of Graves' orbitopathy (divided on the basis of severity of orbitopathy)

Characteristics	Severe GO (n=18)	Mild GO (n=34)	P*
Age (year)	42.4±10.2	39.5±11.0	0.358
Male gender, *n* (%)	10 (55.6)	3 (8.8)	<0.001
Current smoker, *n* (%)	8 (44.4)	3 (8.8)	0.003
Duration of GD (months)	4.2±1.2	2.9±1.6	0.004
Family history of thyroid disease, *n* (%)	5 (27.8)	9 (26.5)	0.920
Pregnancy, *n* (%)	1 (5.6)	2 (5.9)	0.965
Hypertension, *n* (%)	5 (27.8)	12 (35.3)	0.587
Diabetes, *n* (%)	3 (16.7)	8 (23.5)	0.571
Dermopathy, *n* (%)	1 (5.6)	1 (2.9)	0.632
Goiter grade	2.2±0.7	2.0±0.9	0.416
CAS	2.2±0.9	1.3±0.6	<0.001
CAS >3, *n* (%)	5 (27.8)	2 (5.9)	0.029
BMI (kg/m^2)	20.6±4.0	21.8±3.1	0.236
TSH (µIU/mL)	0.012±0.02	0.018±0.03	0.449
Total T4 (mcg/dl)	24.5±5.0	22.4±4.8	0.145
Total T3 (ng/ml)	4.2±1.6	3.6±1.2	0.133
TPOAb titers (IU/ml)	1210±539	1096±426	0.406
TPOAb positivity (>20 IU/ml), *n* (%)	16 (88.9)	29 (85.3)	0.720
TRAb (IU/L) (n=26)	6.2±2.4	3.2±1.6	<0.001
TRAb positivity (>1.5 IU/L) (n=26), *n* (%)	10 (100)	15 (93.7)	0.427
^{99}Tc uptake scan	48.4±8.8	43.9±9.6	0.104
ANC (/mm^3)	1.32±0.5	1.49±0.6	0.309
Neutropenia (<1500/µL), *n* (%)	5 (27.8)	4 (11.8)	0.151
ESR (mm/h)	51.8±12.3	48.3±14.4	0.385
IOP (primary gaze) (mmHg)	19.6±3.6	18.5±4.6	0.382
IOP (upward gaze) (mmHg)	22.8±5.2	19.8±6.3	0.089
Differential IOP >6 mmHg, n (%)	11 (61.1)	5 (14.7)	<0.001

*P<0.05 is considered statistically significant. Categorical variables: *n* (%), continuous variables: mean±SD. SD=Standard deviation, CAS=Clinical Activity Score, BMI=Body mass index, TSH=Thyrotropin-stimulating hormone, TPOAb=Thyroid peroxidase antibody, TRAb=Thyroid receptor antibody, ANC=Absolute neutrophil count, ESR=Erythrocyte sedimentation rate, IOP=Intraocular pressure, GO=Graves' orbitopathy, GD=Graves' disease, T3=Triiodothyronine, T4=Thyroxine

GO ($P = 0.004$). Comorbidities such as hypertension and diabetes and others such as pregnancy and dermopathy were comparable between the two groups. CAS was statistically significantly increased and active (CAS >3) in patients with severe GO as compared to those with mild GO ($P < 0.05$). TSH, total T4, T3, and TPOAb titer and positivity were comparable between the two groups. TRAb was measured randomly in 26 patients because of logistic reasons: 10 in the severe GO and 16 in the mild GO groups. TRAb titer increased in severe GO group (6.2 ± 2.4 IU/L) as compared to mild GO (3.2 ± 1.6 IU/L) group, and the difference was statistically significant ($P < 0.001$). TRAb positivity was similar between the groups. The mean IOP in primary and upward gazes was comparable between severe and mild GO patients. Braley's sign, i.e., the differential IOP of > 6 mmHg between the primary gaze and upgaze, was seen in 61.1% of patients with severe GO and in 14.7% of patients with mild GO, and the difference was statistically significant ($P < 0.001$). There was no statistically significant difference between the two groups with regard to ^{99}Tc uptake scan, ANC, neutropenia, and erythrocyte sedimentation rate.

Factors predicting severe GO are shown in Table 3. On multiple logistic regression analysis, which included all patients with GO, male gender, current smoking, TRAb >2 upper limit of normal (ULN), and differential IOP >6 mmHg were found to be associated with severe GO.

Discussion

The natural course of GO is benign in most patients and improvement is often seen with conservative treatment. However, some patients develop progressive severe orbitopathy and require prolonged steroid treatment, irradiation, or surgical rehabilitation. Clinical decisions would be simpler if the course of GO could be predicted. Several risk factors including old age, male gender, smoking, radioactive iodine, stress, trauma, higher titers of TRAb, and abnormal thyroid function have been identified in several reports as possible predisposing factors for severe GO.

Table 3: Variables predictive of severe Graves' orbitopathy on multiple logistic regression analysis

Variables	*P**	OR (95% CI)
Male gender	0.024	2.90 (1.26-19.52)
Duration of GD (months)	0.051	1.92 (0.53-5.24)
Current smoker	0.015	3.35 (2.84-26.40)
CAS >3	0.054	1.62 (0.43-4.32)
TRAb >2 ULN	0.004	5.62 (3.02-29.44)
Differential IOP >6 mmHg	0.019	3.72 (1.22-24.36)

*P<0.05 is considered statistically significant. CAS: Clinical Activity Score, TRAb=Thyroid receptor antibody, IOP=Intraocular pressure, ULN=Upper limit of normal, OR=Odds ratio, CI=Confidence interval, GD=Graves' disease

In the current study of 52 consecutive patients with GO of Kashmiri ethnicity, GO was mild in 65.4% and moderate to severe in 34.6%. CAS was active in 13.5% of the study group. An Indian study reported that GO was mild in 83%, moderate to severe in 15%, and sight-threatening in 2% of patients.[25] Savku and Gündüz[27] in a study found that GO was active phase in 32.6% and inactive phase in 67.4% of patients. However, in an Indian study by Reddy *et al*.,[25] GO was clinically active in only 3% of cases, while Khong *et al*.[28] in their study reported that CAS was active in 16.5% of cases.

In our study, there was a statistically significant male preponderance in severe GO group ($P < 0.001$). Current smoking increased the risk of severe GO ($P = 0.003$). Duration of GD symptoms at presentation was statistically significantly longer in severe GO patients than mild GO patients ($P = 0.004$). Comorbidities such as hypertension and diabetes and others such as pregnancy and dermopathy were comparable between the two groups. CAS was statistically significantly increased and active (CAS > 3) in patients with severe GO as compared to mild GO ($P < 0.05$). Thyroid status as assessed by the initial T4 and T3 levels was not associated with severe GO. TRAb titer increased in patients with severe GO (6.2 ± 2.4 IU/L) as compared to those with mild GO (3.2 ± 1.6 IU/L), and the difference was statistically significant ($P < 0.001$). TRAb positivity was similar between the groups. Braley's sign, i.e., the differential IOP of >6 mmHg between the primary gaze and upgaze was seen in 61.1% of patients with severe GO and in 14.7% of patients with mild GO, and the difference was statistically significant ($P < 0.001$). In our study, male gender, current smoking status, TRAb >2 ULN, and differential IOP > 6 mmHg were found to be associated with severe GO on multivariate analysis.

Various studies have suggested that moderate-to-severe GO occurs frequently in men,[7,29] while another study[30] did not find any correlation. The apparently greater severity of GO in male patients with GD can be explained by the fact that male patients smoke more than females and males are less likely to present themselves with a "cosmetic" complaint about mild GO. Reddy *et al*.[25] revealed that only in males, smoking and TRAb titer significantly increased the risk of severe GO. Among various environmental factors associated with the increased risk of GO, smoking has been consistently noted[9,10,21,28,31,32] perhaps by causing tissue hypoxia or simply direct inflammation.[31,33]

In Korean patients, being a current smoker was the strongest risk factor for the development of severe GO and dysthyroid optic neuropathy.[22] It was found that cigarette smoke extract increases glycosaminoglycan production and adipogenesis in orbital fibroblasts.[34]

Khong *et al*.[28] identified increased age of onset, duration of hyperthyroidism, and smoking as risk factors for GO. Mathur *et al*.[35] found smoking, male gender, and higher CAS to be associated with severe GO. Lat *et al*.[36] revealed that on multivariate analysis, male gender and elevated TRAb were found to be associated with severe disease (odds ratio [OR] 3.71, $P = 0.041$) and (OR 1.02, $P = 0.007$), respectively. A study in an Asian population failed to identify any relationship between T3 or T4 levels and GO.[37]

A progressively increasing prevalence of GO was observed with increasing TRAb titers, and TRAb titers were an independent risk factor for GO.[6,38,39] TSHR expression is higher in GO orbital fat compared with normal orbital adipose tissues, and there exists a positive correlation between TSHR mRNA levels in individual GO orbital adipose tissue specimens and the patient's CAS.[40,41]

The increase in IOP may be due to tethering by a fibrotic rectus muscle or orbital congestion and venous stasis-limiting aqueous outflow. The clinical sensitivity and specificity of this increase in IOP, especially in upgaze, have been debated, although its existence has not.[42]

This study needs to be considered in light of strengths and limitations. Prospective nature and modest sample size were some of the strengths of the study. The study is also the first of its find from Kashmir, a mountainous northern part of India. The present study had several limitations. First, it was a single-center study; second, there were no patients with sight-threatening GO, which could have altered the significance of various risk factors for GO. Various genetic factors which affect GO were not studied, as Kashmir is ethnically different from India.

Conclusion

Approximately 35% of the patients with GO have severe disease. The current study suggests that like the rest of studies, severe GO is significantly associated with current smoking status in addition to male gender, TRAb >2 ULN, and differential IOP >6 mmHg. Therefore, it is important for patients with GO to refrain from smoking. In addition, frequent and careful observation should be performed in current smokers, as patients who smoke are susceptible to a more severe course of GO.

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Conflicts of interest

The authors declare that there are no conflicts of interests of this paper.

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