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Research Article

A CLINICOPATHOGENETIC STUDY ON GRAVES' ORBITOPATHY IN A TERTIARY CARE HOSPITAL SETTING IN EASTERN INDIA

Madhurima Basak[1], Neha Agrawal[1]*, Sunetra Mondal[1], Subhankar Chowdhury[1] and Sibnarayan Guria[2],

[1]Department of Endocrinology and Metabolism, Institute of Post Graduate Medical education and Research and SSKM Hospital, Kolkata, West Bengal, India
[2]Department of Statistics, West Bengal State University, India

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ABSTRACT

Background: The prevalence of Graves' Orbitopathy(GO) in Indian population is reported to be less, as compared to Caucasians, but there are few and inconclusive data. The role of TRAb in GO development and prediction of activity or severity of GO is not yet clearly understood.
Objective: To evaluate the prevalence and clinico-radiological profile of GO in an Indian cohort and to find out the correlation of TRAb and extra ocular muscle (EOM) thickness with activity and severity of GO.
Methods: Out of 150 patients with GD, 45 treatment naïve patients- 23 with GO and 22 with Graves' disease(GD) without GO were evaluated clinico-radiologically.
Results: 32% had clinical based GO (Mild GO 73%, moderate 26%, sight-threatening 1%). Mean TRAb was slightly higher in GO (24.7133 ± 14.8627IU/l) in comparison to GD (19.8775 ± 10.8022 IU/l, p=0.2469).The presence of GO was significantly associated with smoking [OR: 1.85; 95% CI (-.79 – (-.10), p=0.013] and TRAb positivity [OR: 2.15; 95% CI (.57 – 2.30), p=0.002]. TRAb titers were significantly higher in males and smokers and significantly associated with the degree of proptosis of both eyes. There was no association of TRAb with CAS or degree of severity in GO.GO had increase thickness of recti muscles, determined from MRI, versus GD. The cut-offs for thickness in GO vs GD patients are lower compared to Caucasian data. The values of recti thickness had significant correlation with activity scores (p<0.0001). TRAb correlated with the maximum rectus thickness determined by MRI.
Conclusion: TRAb is an important but not the sole pathogenetic factor in GO. Imaging derived rectus muscle thickness, analyzed with respect to regional normative data is associated with the activity of GO, the maximum rectus muscle thickness being an important parameter.

INTRODUCTION

Graves 'disease (GD) is an autoimmune disease involving primarily the thyroid gland and affecting multiple organs in the body like the eyes. Orbital inflammation resulting from GD , also known as Graves' orbitopathy (GO) results in eyelid retraction, lid lag, lid swelling, erythema, conjunctivitis, and exophthalmos[(1)]. Thyrotropin Stimulating Hormone Receptor antibodies (TRAb) are a set of auto-antibodies which influence thyroid follicular cells causing overproduction of thyroid hormones in GD and also plays a predominant role in the pathogenesis of Graves' orbitopathy (GO)[(1)].The prevalence of GO varies with ethnicity. The annual prevalence of the disease in U.S. state of Minnesota is 16/100,000 in women and 3/100,000 in men[(2)].The prevalence of GO in India is similar to Caucasians of European descent, but clinically active and severe orbitopathy was uncommon among North Indian population with GD[(3)] .About 3–5% of GO patients suffer from sight-threatening corneal ulcer or optic nerve compression. In GO, there is progressive deterioration of symptoms over 3 to 6 months, followed by a plateau phase between 1 and 3 years, then gradual regression toward the baseline[(4)] .This is not yet clearly understood as to why only certain individuals with Graves' disease develop clinically significant orbitopathy. Anatomic, genetic (MHC, CTLA-4,) and environmental factors like smoking, stress, drugs, micronutrients contribute to the development of GO [(5-7)].The pathogenesis of the orbital involvement is explained by the binding of TRAb with TSH-R in extra thyroidal tissues in eye, chiefly fibroblasts and adipocytes in the orbit[(8)] .So TRAb detection is one of the most paramount biomarkers for GD as well as GO development. In the present study, we studied the clinico-radiological profile of patients with Graves'orbitopathy in a tertiary care hospital in India, and tested for differences in biochemical and radiological parameters between GD patients with and without orbitopathy and also whether there is any correlation of TRAb titer or of extraocular muscle(EOM) thickness with the activity or severity of GO.

*Corresponding author: **Neha Agrawal**
Department of Endocrinology and Metabolism, Institute of Post Graduate Medical education and Research and SSKM Hospital, Kolkata, West Bengal, India

MATERIALS AND METHODS

Patients

In this study patients were collected from Department of Endocrinology & Metabolism of IPGME&R Hospital, Kolkata, India from May 2017 to October 2018.Total 150 Graves' Disease patients were collected during this period out of which 45 patients were evaluated further both clinically and radiologically which is maintaining the inclusion criteria. The study was approved by IPGME&R and SSKM hospital ethical committee. Patient history, including diabetes, hypertension, any other autoimmune disorder, family history, smoking status were reviewed. The patients who have received anti-thyroid therapy, radiation therapy immunosuppressive treatment like glucocorticoids, earlier or individuals with other autoimmune diseases, asthma, sinusitis, recent trauma, or HIV infection, malignancy, pregnancy were excluded from this study. Total patient populations were subdivided into two group Group I-22 patients of Graves' disease with out orbitopathy(GD). GroupII-23 patients of Graves' disease with Orbitopathy (GO).Based on the EUGOGO classification (Barrio Barrio J *et al*)[9].severity of GO was graded as mild, moderate-severe and sight-threatening in this study.

Clinical investigation

Clinical examination included weight, height, BMI, thyroid gland for enlargement, nodule, tenderness, and bruit. Height was measured using height recorder (Charder wall-mounted stadiometer (calibrated using a 36" calibration rod [Perspective Enterprise, Portage, Michigan, USA].Weight was recorded by an electronically calibrated scale. Magnetic resonance imaging (MRI) of orbit was performed in all patients. The thickness of each extra ocular muscle (EOM) was evaluated. The horizontal diameters of MR, LR and the vertical diameters of IR were measured in series of images. The largest diameter of the middle section of each muscle was selected.

Assay technique

Serum free T3 (FT3) , free T4 (FT4) and TSH were estimated by CLIA using Immulite 1000, Siemens, USA according to manufacturer's protocol and their normal ranges in adults were TSH 0.4-4 uIU/ml , FT4 0.8-1.9 ng/dl , FT3 1.5-4.1 pg/ml.
Serum TRAb concentrations were assayed by electrochemiluminescence method [ECLIA], which is Cobas e411 of Roche technology. For immunoassay detection, a value ≥1.22 IU/l was considered positive.

Statistical Analysis

Differences in age, duration of disease, proptosis, BMI, CAS scores, TSH, FT3, FT4, TRAb, and EOM thickness seen in MRI between the GD and GO groups were analysed using unpaired t- test. Pearson's or Spearman's correlation was used to determine correlation of TRAb and EOM thicknesses with CAS scores and severity or between TRAb and EOM thicknesses.

Multivariate logistic regression was performed to find out the association between TRAb, age, smoking, sex, duration, FT4, FT3 in between GD and GO. Multivariate regression analysis was performed to find out the association of TRAb with age, sex, EOM thicknesses, TSH, smoking and proptosis. All statistical data were analyzed by SPSS (version24.0; SPSS Inc., Chicago, IL, USA) R studio (Version 3.6.1) and GraphPad Prism version 5 and p-value ≤ 0.05 was considered for statistically significant.

RESULTS

Characteristics of the patients

The demographic , clinical and biochemical data of all 45 patients were shown in Table 1 and ophthalmologic examination findings were summarised in Table 2 below. Values are n (%) or mean ± SD.

There were no significant differences in age, duration of disease, BMI, TSH, FT4, FT3 or TRAb titers between GD and GO patients. Fig 1 shows the distribution of TRAb titer in GD and GO.

The differences between proptosis in both eyes and CAS scores between GD and GO groups were statistically significant (p<0.001, p<0.001, p=0.001 respectively).

Differences of sex and smoking status among GD and GO

Table 1 show the demographic data of the patients

Parameters	GD (N=22)	GO (N=23)	p value (<0.05)
Age	39.3±10.9	33.3±10.8	0.1
Gender	Females=14,Males=8	Females=9,Males=14	0.02*
Smokers Non smokers	8 14	14 9	0.01*
Duration of Hyperthyroid (in months)	4.5 (1-24)	5(1-36)	0.001*
BMI [in kg/m2]	18.80(14.30-25.80)	17 (14-28)	0.86
Proptosis [Right eye]	16 (14-17)	19 (17-24)	<0.001*
Proptosis [Left eye]	16(14-17)	20 (18-24)	<0.001*
CAS	0	1 (0-5)	0.001*
TSH(uIU/ml)	0.01±0.01	0.01±0.01	0.92
FT4(ng/dl)	4.4±1.5	4.4±2.13	0.7
FT3(pg/ml)	10.7±5.7	11.3±7.11	0.7
TSH-R antibody(TRAb) (IU/l)	19.8±10.8	24.7±14.8	0.1
Severity (in GO)	-	Mild 13 Moderate 10	-

* Indicates the statistically significant values

In the GD group, 64% patients were females, 36% patients were males and 36% patients were smokers. In the GO group, 39.1% patients were females and 60.8% patients were males with 60.8% being smokers. All the smokers were males. The differences in sex and smoking status between the two groups were significant (p=0.02, p=0.01respectively).

Table 2 show the ophthalmologic examination of the patients

Characteristics	Number of patients(n=23)
Unilateral eye involvement	2(9.5)
Upper eyelid retraction	18(86)
Lower eyelid retraction	14(67)
Exophthalmos	
<20mm	13(61.9)
≥20mm	8(38.1)
Exophthalmometric value of most affected eye (mm)	20.09±1.4
Soft tissue involvement	12(57)
Lagophthalmos	6(28.6)
Corneal involvement	0
Optic nerve dysfunction	0
Severity	
Moderate-severe	8(38.1)
Sight –threatening	0(0)
Clinically active disease(CAS 3-7)	1(4.8)

Relationship between CAS scores, severity of GO and TRAb levels

There was no patient with sight threatning GO or CAS score > 3. GO patients were divided further into CAS0(CAS score = 0) and CAS123 (CAS score > 0 and <=3) groups. In the CAS0 group, 6(66.6%) patients had mild severity and 3(33.4%) patients had moderate severity. In CAS 123, 7(58.3%) patients had mild severity and 5(41.7%) patients had moderate severity. There were no differences of severity in the two CAS groups (p=0.69). The mean TRAb of patients in CAS 0 and CAS 123 was 18.53 ± 14.66 IU/ml and 29.34 ± 13.80 IU/ml respectively. A positive but statistically insignificant correlation was found between TRAbtiters with CAS scores in GO group (p=0.3) (Fig 5). The mean TRAb of mild cases was 22.59 ± 16.22 IU/ml vs 28.16 ± 12.56 IU/ml in those with moderate GO (p=0.418).

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Association of TRAb with multiple clinical and biochemical variables

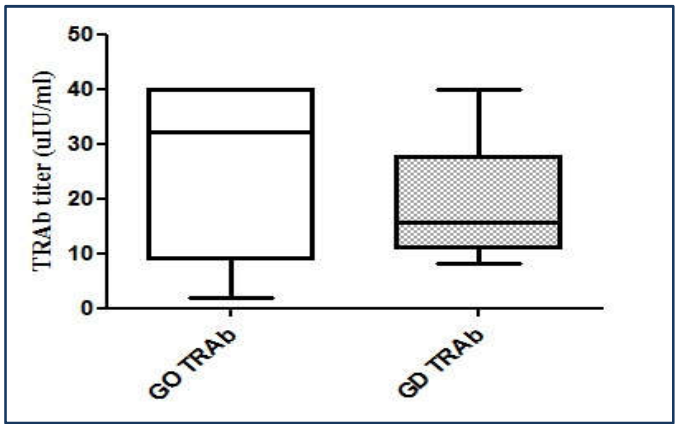

Figure 1 TRAb titer in GD and GO (p=0.15)

In Figure 1 TRAb titer was slightly higher in GO compared to GD but this difference was not statistically significant. In the GO group, TRAb titer was also significantly higher in males and smokers compared to females and non-smokers.

In multivariate logistic regression analysis in table 3 we also found that in male who were smokers, TRAb titer was higher compare to female and non-smokers. So male and smoking status were significantly associated with the increasing of TRAb titer and help in the pathogenesis of GO

Table 3 Multivariate logistic regression analysis of sex, smoking status and TRAb titer in GO

Parameters	Odd Ratio (OR)	95%CI	P value (<0.05)
Sex	9.42	-9.52-(35.28)	0.001
Smoking	1.81e+05	-4.47-(28.69)	0.02

In multivariate regression analysis we found that TRAb titer was also significantly and highly associated TSH [Odd Ratio (OR) : 3.19e-272 ;95%CI (-1.23)-(-16.65) p=0.01]proptosis of left eye [OR: 6.31;95% CI (-1.25)-(2.43), p=0.01] and proptosis of right eye [OR:1.18e+01;95% CI (-3.60)-(14.15)p=0.01] in GO.

In GD though TRAb titer was associated with proptosis of left eye [OR: 2.77; 95%CI (-11.09)-(17.74) p=0.09], proptosis of right eye [OR:3.35;95%CI (-16.65)-(23.67) p=0.19],TSH [OR:3.06;95%CI (-103.38)-(451.01) p=0.09] but they are not statistically significant.

Relationship of multiple clinical and biochemical parameters with the presence of GO

Using multivariate logistic regression analysis, we found a significant association of smoking [OR: 1.85; 95% CI (-.79) – (-.10), p=0.013] and TRAb positivity [OR: 2.15; 95% CI (.57) – (2.30), p=0.002] with the presence of GO. FT3, FT4 levels were not significantly associated with the presence of GO. Duration of symptoms and sex were not significantly related to GO.

Radiologic findings - EOM thickness in GD and GO

The thickness of medial rectii (MR) of both left(L) and right (R) sides - MR(L), MR(R) and also, inferior recti (IR) of left(L) and right (R) sides- IR (L) and IR (R) were significantly higher in GO patients versus the GD patients. Though lateral rectus (LR) is known to be less frequently involved in GO, interestingly, in our study, LR thickness of both eyes were significantly higher in GO patients than GD patients as well. We calculated the average thickness (illustrated in figure 3)of MR of both sides ATMR(Average thickness of bilateral medial recti) = {MR(L) + MR(R)}/2. Similarly, we calculated the ATLR (Average thickness of bilateral lateral recti) and ATIR (Average thickness of bilateral inferior recti). GO patients had significantly higher ATMR, ATLR and ATIR than GD patients. We used EOMmax to denote the thickness (in mm) of the muscle which is thickest out of the six recti muscles (three in each eye) for each individual patient. The median EOMmax of GO patients was 5 mm (range 3 – 7.1) versus 3.5 mm (range 2 – 4.5) in GD patients without orbitopathy (p=0.0002).

Using Receiver Operating Characteristic (ROC)curves, we determined the best possible cut-offs of muscle thickness of the recti - ATMR, ATLR ,ATIR and EOMmax which could best distinguish GO patients from GD in our cohort. These cut-offs are summarised in Table 4. A notable finding was that our cut-offs for the thickness of each rectus muscle or the average of a pair of recti was much lower than the existing reference of 4 mm which is currently used to denote increased thickness in GO patients . The best ROC with the largest area under the curve (AUC) was obtained for EOMmax with an AUC of 82.6% ,p=0.0002 and a cut-off value of EOMmax 3.95 mm can distinguish GO patients from GD patients with a sensitivity of 75% and specificty of 81%.(Figure 2)

Table 4 Cut-offs of different EOM thickness parameters in distinguishing GO from GD

Parameter	GO (Median)	GD (Median)	AUROC (%)	Cut-off(mm)	Sensitivity	Specitivity	p value
Average of both medial recti (mm)	3.75 (2-5.15)	3(1.75-4)	81	3.4	76.2	85	<0.0001
Average of both inferior recti (mm)	4.6(3- 6.7)	3.05(2-4.4)	81.4	3.6	80	71.4	0.003
Average of both lateral recti (mm)	4 (2-5.5)	3.05 (2-4)	78.5	3.55	75	76.2	0.013
Maximum rectus muscle thickness (EOMmax)	5(3-7.1)	3.55(2-4.5)	82.6	3.95	75	81	0.0002

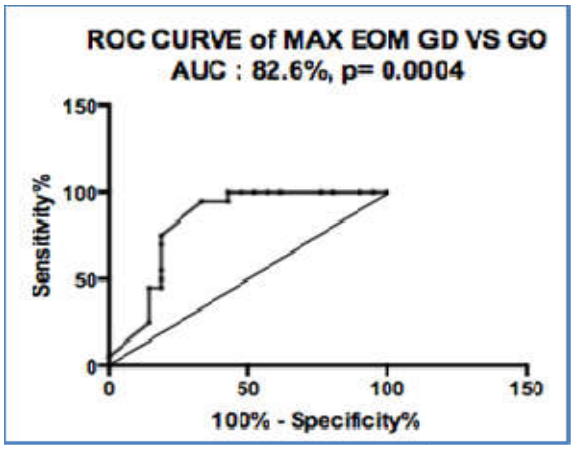

Fig 2 ROC curve for Max-EOM

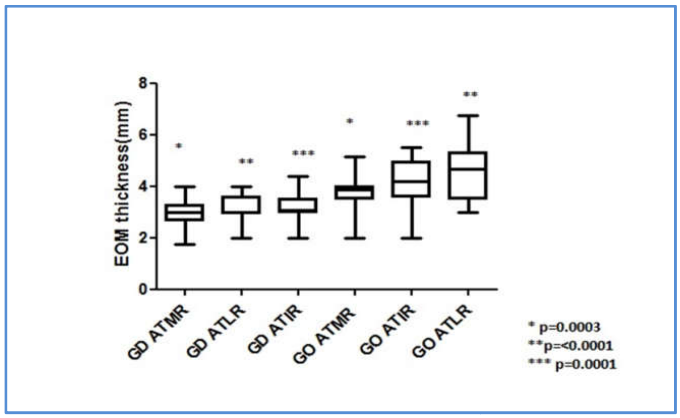

Figure 3 EOM thickness for different muscles in GD and GO

In multivariate regression analysis we found that TRAb titer was also significantly and highly associated with Max EOM thickness [OR: 1.12e+01; CI (-3.78)-(8.62), p=0.04]in GO but in GD though TRAb titer was associated withMax EOM thickness [OR:7.49; 95 %CI (-1.01)-(18.86),p=0.07] but it was not statistically significant.

There was significant correlation of the values of ATMR,ATIR,ATLR, EOM max and the sum of the thickness of the six recti muscles with the CAS scores (r=0.81,0.80,0.67,0.47 and 0.49 respectively, pall<=0.001) However, there were no significant differences of any of the values between the groups with moderate or mild severity of GO.

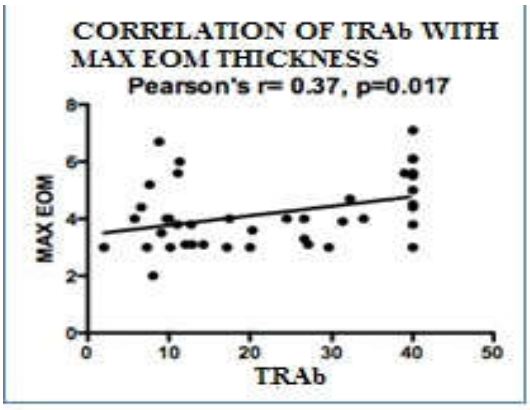

Figure 4 Correlation of TRAb titer withmax EOM

In our study, there was no significant correlation of TRAb with CAS scores or the degree of severity. TRAb didn't have a correlation with thickness of MR or LR. However, we found a significant positive correlation of TRAb with ATIR (p=0.02, Pearson's r =0.33) and with EOMmax (p=0.017, Pearson's r = 0.37), as outlined in Figure 4. The correlation between TRAb and sum of the recti thicknesses neared significance (p=0.07).

DISCUSSION

In our study, out of 150 consecutive adult patients with GD, 102 cases (68%) had GD without GO, 48 cases (32%) had a clinical diagnosis of GO of which 35 (73%) cases had mild activity while 12 (25%) had moderate-severe active GO and 1(2%) case had sight-threatening . The present study noted an overall 32% prevalence of GO among GD patients. Prevalence of GO reported by previous Asian studies were 34.7% (Lim *et al*)[10] , 28%(Reddy *et a*l) [3] ,37.3% (Subetki *et al*)[11] . The results of various studies must be interpreted cautiously, as these studies have used different clinical and diagnostic criteria. Tellez *et al*[12]noted a higher prevalence of GO in Caucasians compared to Asians (42% vs 7.7%) but they had only 39 out of the 150 subjects as Asians. So, the current study does not agree with the current concept that GO is uncommon in Asians. Our findings (32%) are comparable to that reported for Caucasians (25-50%).

As TRAb titer usually decreases during treatment with antithyroid drugs, it becomes difficult to evaluate the correlation between GO activity and TRAb titer after starting antithyroid drug therapy. Therefore, we selected untreated Graves' disease patients with/without GO as the subjects of our study. In current study, in comparison to GD, GO patients had a slightly earlier age of presentation. Similar results have been reported by Reddy *et al*[3].

There was female preponderance in GD (70%) whereas GO patients were predominantly males (61.9%). Amongst the treatment naïve GO patients in our study, 61.9% patients had mild severity with CAS ranging from 0-2 and 38.1% patients had moderate severity with CAS scores between 0 to 3 and none had sight threatening disease. In contradiction, EUGOGO included 152 European patients with GO where 28% had severe and 33% had moderate disease and 60% had clinically active disease[13] .It has been shown that Europeans are at higher risk of developing active and severe GO than Asians[14]. Possible reasons for the less severity of GO in our patients could be lesser smoking rate and a more favorable orbital or

craniofacial bony structure in Asians. Upper eyelid retraction, exophthalmos and soft tissue involvement were the common clinical features, which corroborated with a prior Indian study[15] . Compared to Caucasians, diplopia was rare in our study[16] In contrast, in a multi-ethnic Asian study, lower eyelid retraction and proptosis were the most common features[10]. A EUGOGO study observed soft tissue inflammation with highest frequency (75%)[13]. Reasons for this clinical variability are unknown.

In our study, the mean TRAb was non-significantly higher in GO as compared to GD without orbitopathy. Similar finding was seen in Khin Swe Myint *et a*l [17] But Reddy *et al*[3] found higher TRAb in GD with GO as compared to those without Orbitopathy. Although TRAb is known to be a chief pathogenic mediator or orbital inflammation, a significant correlation between TRAb titer and GO activity or severity was not seen in this study. Similar results were evident in several prior studies[3,11]. However, Mukasa K *et al*[18] found higher TRAb titer in inactive GO than in active GO . Apart from the limitation of a small sample size, none of our patients had CAS score of > 3, which is the EUGOGO cut-off for glucocorticoids or other immunosuppressants. Therefore, the clinical relevance of this finding is unknown.

Also, while TRAb may be a chief casuative factor for GO, there must be other factors involved in its progression including the expression of TSH-receptors, co-localization of IGF-1 receptors and Th1-derived cytokines, particularly in the active stage of GO[19]

We found a lower cut-offs for the thickness of the recti muscles as compared to the existing cut-off . Studies have shown an overall lower normative values of EOM in the Indian population versus Caucasians. [20]

We found increased thickness of EOM – specifically, the medial, inferior and lateral recti, in GO as compared to GD, which was statistically significant. There was also a significant correlation of the averaged thickness of bilateral medial recti, average thickness of both inferior recti, average of bilateral lateral recti thickness, the maximum of the EOM thicknesses and the sum of thickness of the six recti muscles with the CAS scores. However, we did not find an association of EOM thickness with severity of GO. EOM thickness of all (MR, IR, LR) muscles were positively correlated with TRAb, however it was statistically not significant, except for the averaged thckness of bilateral inferior recti. However, TRAbtiters did correlate significantly with the value of maximum thickness among the recti muscles for an individual with GO.

Kvetny *et al*[21] reported that in newly diagnosed severe GO, the EOM volume correlated with TRAb values, CAS and proptosis. Hiromatsu *et al*[22] ; Nishikawa *et* al[23] showed remarkably positive correlations with EOM volume and severity of eye disease, duration of eye symptoms and TRAb . Zimmermann-Belsing *et al*[24], studied four horizontal rectus muscle thicknesses by ultrasonographic- B scan and reported that muscle thickness did not correlate with thyroid autoimmune activity (TRAb and TPOab). In contrast, our study had majority of inactive mild cases and instead of volume, we measured the muscle thickness. It also seems to be that there is no comparison between results obtained with ultrasonography and those obtained with MRI. Overall results from this study suggest that thickness of recti muscles seen radiographically could be a predictor of activity but not severity of GO even in cases with low CAS scores. Also, the EOM with maximum thickness would be more important rather than its location given that the parameter EOMmax served as the best distinctor of GO from GD without orbitopathy, had good positive correlation with both TRAb and CAS scores and that lateral rectus was also frequently thickened in our cohort. As compared to TRAb, imaging derived values of recti muscle thickness could better identify patients at greater risk of developing active GO before it is clinically evident from their CAS scores. Indian GO patients likely have lower cut-offs for thickness of the recti muscles and needs more and accurate normative data.

Although differences in TRAb titer among GD and GO was not statistically significant but after using multivariate logistic regression study we identified that TRAb titer, smoking and age had statistically significant relation with GO. AK Eckstein *et al*[25] performed similar regression and revealed that TBII, smoking status, and age all have significant influence on the course of GO.

The results of the current study, seems to downplay the role of TRAb in the pathogenesis of GO. While an obvious limitation was a small sample size, it hints at the role of other factors like TSH – receptor expression and other potential orbital antigens like thyroglobulin and cholinesterase epitopes, in the pathogenesis of Graves' Orbitopathy.

CONCLUSION

The prevalence of severe or more active GO is probably lower in Indian patients with Graves' disease. While TRAb is an important factor in the pathogenesis of GO, it maynot always correlate with the activity and severity of GO hinting at the role of other agents. Rectus muscle thickness values obtained from orbital imaging , particularly the value obtained for the rectus muscle with the maximum thickness, is associated with activity of GO. Pending further longitudnal studies, it might predict active GO even in patients with low clinical activity scores. The muscle thickness should be interpreted in accordance with regional normative data.

Disclosures

The Authors state that they do not have conflict of interest.

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