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Original Research Article

Correlation of clinical parameters and objective assessment tools in active thyroid eye disease – Prospective analytical study

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ABSTRACT

Aim: Primary objective of this study was to identify the disease in active phase, clinically assess it and start medical management. Secondary objective was to analyze whether the objective tools like B-scan and serum levels of IL-6 and HS-CRP aid in the diagnosis of activity in thyroid eye disease.

Materials and Methods: The aim was to analyze the correlation of clinical parameters and significance of objective assessment tools in active thyroid eye disease. Clinically diagnosed cases of TED with lid signs, soft tissue changes, restrictive myopathy and bilateral axial proptosis were included in our study. Patients in chronic stable phase were excluded from study. This was a prospective analytical study, conducted from June 2010 till June 2012. Sample size was thirty patients in the age group of 20 to 60 years. Complete ophthalmology workup and objective disease assessment tools including B scan (OTI 1000 with 7.5-10 MHz) was used in our study. All patients underwent CT scan orbit-axial and coronal view. After assessing the severity and stage of the disease, each patient was managed accordingly using different modalities.

Conclusion: Identifying the disease activity early and aggressive management with systemic steroids in moderately active and severe stage has decreased the morbidity associated with the disease. A- scan with orbital B-scan helps in diagnosing the activity in thyroid eye disease. This procedure is very economical with relatively short examination time and no risk of radiation .Follow up of the patients can also be performed easily. IL-6 and HS-CRP was statistically significantly elevated in patients with severe disease when compared to control group. Hence can help in assessing disease activity in patients with severe disease.

1. Introduction

Thyroid eye disease (TED) also known as Graves Orbitopathy, is typically self-limiting autoimmune process associated with dysthyroid status. Incidence of TED is 90% in Graves' disease, 3% in Hashimoto's Thyroiditis, 1% in primary Hypothyroidism, and 6% in Euthyroid status and at least 50% of these patients develop clinically evident symptomatic TED. The patients may present as mild disease to severe irreversible disease.[1] In 5-10% of patients vision loss occurs due to corneal decompensation or optic nerve compression. TED affects women 2.5-6 times more frequently than menm[1,2] in older age female: male ratio decreases. The peak incidence is in second to fifth decade, severity increases with older than 50 years. Smoking is strongly associated with TED due to generalized stimulation of autoimmune disease and effect of hypoxia on orbital fibroblast. Diabetics tend to have more severity in TED. In this study various parameters are studied and correlated

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to understand the disease activity in different stages with various manifestations.

2. Aim

Primary objectivewas to identify the disease in active phase, clinically assess it and start medical management. Secondary objective: To analyze whether the objective tools like B-scan and serum levels of IL-6 & HS-CRP aid in the diagnosis of activity in thyroid eye disease.

3. Materials and Methods

The study was initiated after obtaining clearance from Institutional Ethics Committee. The aim was to analyze the correlation of clinical parameters and significance of objective assessment tools in active Thyroid Eye Disease. Clinically diagnosed cases of TED with lid signs, soft tissue changes, restrictive myopathy and bilateral axial proptosis were included in our study. Patients in chronic stable phase were excluded from study. This was a prospective analytical study, conducted from June 2010 to June 2012. Sample size was thirty patients in the age group of 20 to 60 years. Evaluation was carried out for patients presenting initially or referred from endocrinology department as a known case of hypo/hyperthyroidism, detailed history taking with regard to disease onset, duration and rate of progression of the disease, history of smoking and history pertaining to ocular symptoms like pain, redness, foreign body sensation, photophobia, defective vision, double vision were noted. Complete ophthalmology workup included visual acuity, lid signs, slit lamp examination of anterior segment, pupillary reaction, extraocular movements, fundus examination, fields, colour vision, diplopia charting, Schirmers test, Hertels Exophthalmometry, differential intraocular pressure measurement and forced duction test were done. Blood tests included serum level-IL6, HS-CRP, RBS, serological test-Free T3, T4, and TSH. Categorizing the patients as clinically active if Clinical Activity Score (CAS SCORE) is 4 or more and severe based on the parameters like proptosis, diplopia and optic neuropathy. Objective disease assessment tools including B scan (OTI 1000 with 7.5-10 MHz) were used in our study that provide topographic information of extraocular muscles using medium gain setting with patient fixating in primary gaze and longitudinal mode with probe placed opposite to the muscle being examined. Internal structure and reflectivity were evaluated in anterior 1/3rd -1/2 0f muscle. Double peaked sheath spikes indicate that perpendicularity is achieved. Tendon sparing muscle enlargement with corresponding low reflectivity is observed in the A scan. All patients underwent CT scan orbit-axial and coronal view for the evidence of Tendon sparing extraocular muscle enlargement with apical crowding or fat hypertrophy was observed. Biochemical parameters evaluated include IL-6, HS-CRP, TFT was done and their correlation with activity of TED was analyzed. The serum samples of patients in moderate and active stages are taken and IL-6 and HS-CRP using ELISA were done. The results were compared with patients in control group without TED. The patients diagnosed clinically with TED were categorized as mild, moderate and severe activity. Endocrinologist opinion was obtained for all patients and treatment of systemic thyroid dysfunction was started. Thyroid status was kept under control and advised to stop smoking. Patients in mild stage were given supportive management like topical lubricant eye drops, head end elevation. Patients are followed up every 6 months and monitored clinically for disease progression. Patients in moderately active stage were treated with oral Prednisolone 1mg/kg body weight given for 4-6weeks and followed up every 2 weeks to assess the disease activity, visual acuity, pupil for RAPD, extraocular movements and Hertels exophthalmometry were performed. If patients are symptomatically better with resolving signs of activity the steroids are continued in the same dosage for 2 weeks and then tapering is done. Patients in severe active stage based on subjective ocular symptoms and clinical features like soft tissue signs with extraocular movement restriction with diplopia, severe proptosis and compressive optic neuropathy. Radiological evidence showing apical crowding and A scan showing low eye muscle reflectivity were started with IV pulse therapy with Methyl prednisolone 1gm diluted in 500ml normal saline infused over 30 minutes for three days and patients are discharged with oral steroids (40- 60mg). Patients are reviewed every week for signs of activity, optic nerve compression and steroid side effects.

4. Results

A total of 30 patients in the age group of 20-60 years with thyroid eye disease were studied over the period of two years for age at presentation, sex incidence, presenting clinical features, thyroid status and disease activity, associated risk factors. All the patients underwent detailed clinical evaluation, supportive investigation was done and treatment was recorded. Of the 30 cases examined, most common age group was between 20-30years (33.33%) (Figure 1), females (60%) are most commonly affected than males. The disease process was most common in Hyperthyroid (83.33%) patients as compared to Hypothyroid (3.33%) and Euthyroid status (13.33%). Risk factors associated with TED in our study were smoking in 30% and Diabetes Mellitus in 6.66%. 70% patients had bilateral and symmetrical involvement whereas 30% presented asymmetrically. Proptosis with lid retraction was the most common initial presentation. Subjective symptoms like oppressive retro orbital feeling and pain on eye

movement was present in all our patients. Objective signs like Conjunctival congestion were present in 73.33% and Eyelid swelling in 33.33%. Severe proptosis >23mm was present in 20% and soft tissue features were present in 50% of our patients. Extraocular movement restriction was found in 50% of patients in moderate and severely active patient, associated with diplopia only in 10% patients, (Table 1) and differential IOP of >4mm difference in about 20% 0f them. Visual acuity with Snellen chart showed 6/6 in 83.33%, 13.33% patients had 6/18-6/12 due to cataractous changes, 3.33% patients with vision <1/60 which was due to associated Retinitis Pigmentosa and cataract. Patients presenting with clinical activity score >4 were categorized as moderately active in 30%, severe disease in 20% (Figure 5), mild stage in 50% of patients. CT ORBIT axial and coronal view showed tendon sparing muscle enlargement in 40% of patients and fat hypertrophy in 10% of patients. Fat hypertrophy was more common in younger patient (Figure 2). B SCAN- Tendon sparing EOM thickening was found in longitudinal mode and the maximum muscle belly was measured, corresponding low eye muscle reflectivity was noted in A scan. Inferior rectus was most frequently involved (50%) followed by medial rectus (30%) and LPS –SR complex (20%) (Figure 3). The patients in moderate and severely active stage, IL-6 and HSCRP were done which were compared with control group without TED and the results were analyzed using ANOVA followed by the TURKEY HSD test. The P value was significant at 5% level for both IL-6(0.013) and HS-CRP (0.041) in severely active patients and was not significant in moderate activity group. The mean difference was significant at 0.05 level with the P value of .016 when severe group was compared with moderate and control group and not significant when moderate group was compared with control group. 50% of the patients presented with mild disease and were treated with supportive therapy. Moderately active patients (30%) were treated with oral steroids and 20% of the patients in severely active phase were treated with pulse Intravenous Methylprednisolone followed by oral steroids (Figure 4). Follow up showed remission in 86.66% patients in mild and moderately active stage where as 4 patients in severe stage treated with iv methylprednisolone pulse therapy showed exacerbation after 6months.Those patients were treated with pulse therapy again, followed by oral steroids. Remission was attained in all our patients with steroid treatment, Eyelid retraction remained the same in all patients.

5. Discussion

In the present study, total number of 30patients in the age group of 20-60 years with clinical features of active Thyroid Eye Disease were examined for the following: The mean age of presentation in our study is 38.86. Most

Table 1: Clinical manifestations and its ratios in study population

Clinical manifestation	No of patients	Percentage
Lid signs	30	100%
Soft tissue inflammation with CAS >4	15	50%
Ocular movement restriction	15	50%
Diplopia	3	10%
Active stage		
Mild	15	50%
Moderate	9	30%
Severe	6	20%
Optic nerve compression	-	-
Differential IOP >4mm	6	20%
Proptosis >23mm	6	20%

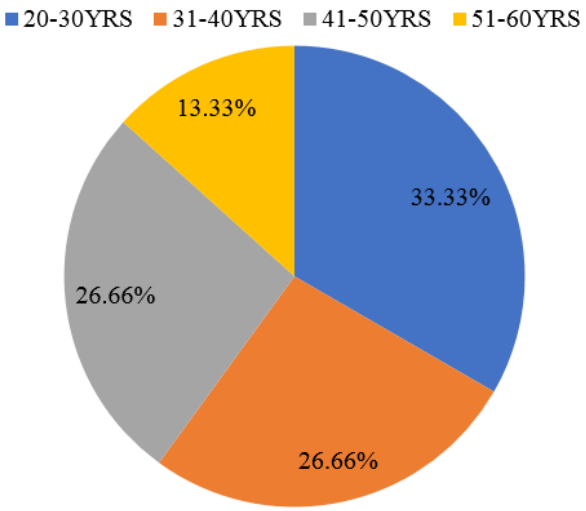

Fig. 1: Age distribution

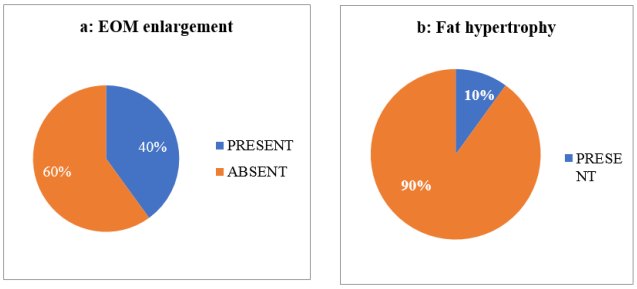

Fig. 2: CT Scan findings

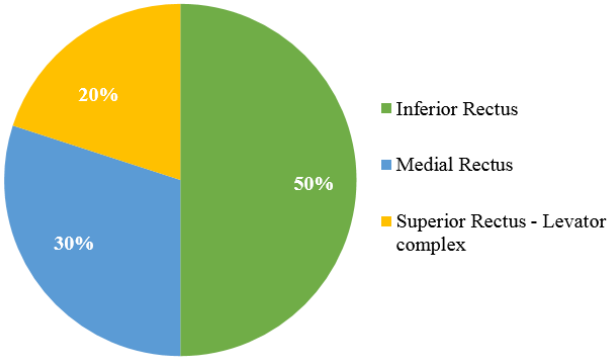

Fig. 3: B Scan -EOM involvement

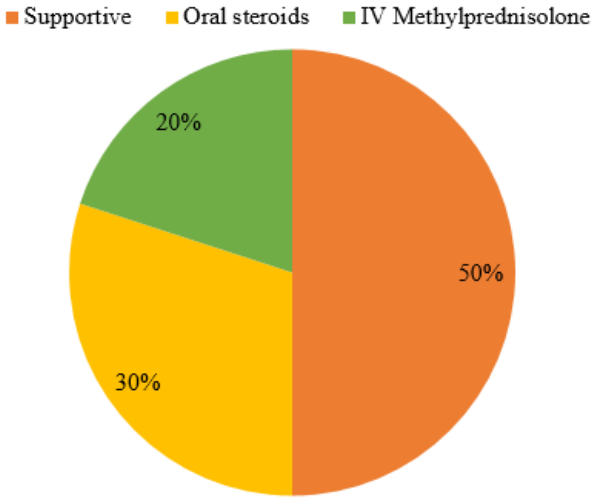

Fig. 4: Modes of management

Fig. 5: Patient in severe stage of disease showingproptosis and congestion

common age group being 20-30 years (33.33%). Our study was compared with study by Bartelena et al which showed two peak incidences $5^{th}$and 7^{th} decades.[3] In our study there were 60% females and 40% males. The female: male ratio is 1.5 and the ratio is 0.5 in severe forms of disease which was correlating to the study conducted by Prummel et al and Haage E et al.[4] Our study shows that males have severe form of disease in 66.66% as compared to females 33.33%, with the associated smoking as risk factor. It is compared with the study by Haage E et al.[5] which showed Cigarette smoking plays an important role in the occurrence of ophthalmopathy and is also associated with a higher degree of disease severity and a lower effectiveness of its medical treatment.[4] Diabetes was present in 6.66% of patients in our study which was correlating with the study done by Prummel et al.[6] which showed 10% association with TED and considered it to be a significant risk factor. In our study the disease process was most common in 83.33% of hyperthyroid patients, 3.33% in hypothyroid patients and 13.33% of euthyroid patients and these parameters were comparable with the study conducted by Prummel et al. Another study conducted by Bartley et al[7] showed that Graves ophthalmology was more frequent in hyperthyroidism (90%), 3% in hypothyroidism and 6% in euthyroid which was also correlating with our study. 70% patients had bilateral and symmetrical involvement whereas 30% presented asymmetrically. The study was comparable with the study conducted by Bartley et al.[7] In our study proptosis with lid retraction was most common initial presentation. Subjective symptoms like Oppressive Retro orbital feeling and pain on eye movement was present in all our patients.[7] Objective signs like Conjunctival congestion was present in 73.33% and eyelid swelling in 33.33%.Severe proptosis >23mm was present in 20%. Extraocular movement restriction was present in 50% but 10% presented with intermittent diplopia, the differential IOP elevation >4mm was found in 20% of these patients which is correlated with the study by Bartley et al[7] which states that 50% of orbitopathy presents with motility restriction. Soft tissue features were present in 50% of our patients which was compared to the study by Kendler et al[8] and Bartley et al,[7] which showed association of soft tissue features in 34-75%. In our study, 83.33% of patients presented with 6/6 Vision with correction, 6/18-6/12 in 13.33% which was due to cataractous changes and 3.33% with vision <1/60 which was due to associated Retinitis pigmentosa and cataract. No patient presented with vision loss due to optic nerve compression or corneal involvement in our study. Patients were categorized as mild by insidious onset, lid lag, lid retraction, minimal proptosis, moderately active based on lid signs, soft tissue changes, moderate proptosis with intermittent myopathy, imaging showing disproportionate proptosis with mild extraocular enlargement. Severe stage is characterized

by rapid onset with predominant inflammatory and mass effects, progressive myopathy and compressive optic neuropathy, imaging showing evidence of extraocular muscle enlargement with apical crowding. Patients presenting with clinical activity score >4 was categorized as mild stage in 50% of patients, moderately active in 30% and severe disease in 20% of patients. Our study was correlating with the study conducted by Bartley et al.[7] The B scan was done in longitudinal mode and the extraocular muscle thickness was compared with normative data given by Byrne et al.[9,10] Inferior rectus was most frequently involved about 50% followed by medial rectus 30% and LPS-SR in 20% of our patients. Our study was comparable to the study by EV Nagy et al[10,11] which showed that the inferior rectus (93%) were the most frequently enlarged, Medial, lateral and superior recti were enlarged in 59%, 37% and 34% of the orbits respectively. CT orbit was done for all the patients. Extraocular muscle enlargement was present in 40% patients and fat hypertrophy in 10% of patients. The fat hypertrophy was more frequent in young individual. Our study correlates with the "Graves Orbitopathy - Current Imaging procedures" by Berhard Krish et al.

Biochemical investigation included TFT, IL-6, HS-CRP. The serum samples of patients in moderate and severe stage were taken and IL-6 and HS-CRP was done using ELISA technique and the results were compared with control group without TED. The results were analyzed using ANOVA followed by TURKEY HSD test. The P value was significant at 5% level for both IL-6 and HSCRP[10] in severely active patients and was not significant in moderate activity group. The mean difference was significant at 0.05 level when severe group was compared with control group and not significant when moderate group was compared with control group. There was no correlation between IL-6 and HS-CRP in the same group. Similar study conducted by Prummel et al states that proinflammatory cytokines like IL- 1b, IL-6 and IL-10 are elevated in active TED when compared to inactive stage.[12] Another study by Molnar and Balazs[13] found that significantly increased serum IL-6 was found in Graves Ophthalmopathy and suggested that IL-6 may be an important factor in the inflammatory events of Graves' ophthalmopathy.

The patients in mild stage of the disease (50%) were treated with supportive therapy like topical lubricants and head end elevation.30% of patients in moderately active stage were treated with oral steroids and 20% of them in severe stage with IV Methyl Prednisolone pulse therapy 1gram in 500ml of normal saline for 3 days followed by oral steroids 40-60mg. followed weekly and assessed for disease activity for first 4 weeks. The patients in mild stage who were treated with supportive management were followed up every 6 months, moderate and severely active patients who were put on either oral or intravenous steroid respectively were followed up weekly and biweekly respectively till 4 weeks to assess the response to treatment. Visual acuity, slit lamp examination, differential IOP, fields, colour vision, Hertel's exophthalmometry, Blood Pressure recording, Random Blood glucose and systemic side effects of steroid therapy were monitored. Follow up showed remission in 86.66% patients in mild and moderately active stage where as 13.33% patients in severe stage treated with IV Methylprednisolone pulse therapy showed exacerbation after 6 months. Those patients were treated with pulse therapy again, followed by oral steroids. Remission was attained in all our patients with steroid treatment. The study conducted by Thambe K Bargawa concluded that IV Methylprednisolone is more effective in moderate and severely active TED patients.[14,15] Eyelid retraction remained the same in all patients and were symptomatically better, inflammatory signs were reduced and disease progression was curtailed. The patients were then followed up monthly for 6 months and 3 monthly thereafter for 1 year.

6. Conclusion

Clinical assessment remains the paramount importance in diagnosing the activity in Thyroid Eye Disease although controversies do exist in clinical evaluation and management. A scan with orbital B scan aids in the diagnosis of thyroid eye disease in active stage, which is very economical with relatively short examination time and no risk of radiation. Follow up of the patients can also be performed easily. IL-6 and HS-CRP was statistically significant at 5% in patients with severe disease when compared to control group. The correlation between HS-CRP and IL-6 in all three groups were not significant. Though the parameters show the significance for severe disease, its role in moderate disease could not be assessed. Identifying the disease activity early and aggressive management with systemic steroids in moderately active and severe stages has decreased the morbidity associated with the disease.

7. Conflict of Interest

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

8. Source of Funding

None.

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