STUDY OF CORRELATION AND SIGNIFICANCE OF BIOCHEMICAL PARAMETERS IN THE ASSESSMENT OF ACTIVE PHASE OF THYROID EYE DISEASE

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ABSTRACT

AIM

Role of Interleukin-6 and HS-CRP Levels in the assessment of active thyroid eye disease.

MATERIALS & METHODS

A prospective observational study of 30 patients from the age group of 20-60 years with thyroid eye disease done at Regional Institute of Ophthalmology. All patients were subjected to detailed history, ocular examination, systemic examination, biochemical analysis and Imaging. Patients are categorised as mild, moderate and severe active disease based on clinical activity score. For the period of two years, patients are followed at regular periodic intervals according to the severity of disease and results were analysed.

RESULTS

Out of 30 patients studied, majority of the patients were females (60%), and 70% of the patients had bilateral disease. Among 30 patients, 83.33% in hyperthyroid state, 3.33% in Hypothyroid state, 13.33% in Euthyroid state (Table 3). Smoking being important risk factor in 30% among males. 50% of patients presented with mild disease, 30% with moderate disease, 0% with severe disease. IL-6, HS-CRP levels are increased only in patients with severe active disease (Table 6). Remission attained in all patients when treated earlier with steroids.

CONCLUSION

Identifying disease activity early and aggressive treatment with systemic steroids in active phase of moderate and severe disease has reduced the morbidity associated with disease. Correlation of IL-6, HS-CRP, TFT levels are significantly increased only in patients with active phase of severe thyroid eye disease but not significantly elevated in active phase of moderate disease. Another pitfall is IL-6 is an expensive ELISA based diagnosis. Thus, IL-6 & HS-CRP cannot be routinely used to screen patients with Thyroid eye disease.

KEYWORDS

Proptosis, Active Thyroid Disease, Compressive Optic Neuropathy.

HOW TO CITE THIS ARTICLE: Ashok Kumar P, Ramapriyadharshini J, Subhashini M. Study of correlation and significance of biochemical parameters in the assessment of active phase of thyroid eye disease. J. Evid. Based Med. Healthc. 2016; 3(70), 3803-3808. DOI: 10.18410/jebmh/2016/814

INTRODUCTION: Thyroid disease associated with ocular changes were first published by Graves in 1835 and by von Basedow in 1840. Caleb Parry showed the association between eyeball enlargement and goitre in 1786. It remains the most common cause of unilateral or bilateral proptosis. Thyroid eye disease[1] is usually a self-limiting autoimmune process associated with dysthyroid status. Females are affected 5-6 times commonly than males. Incidence of TED is about 90% in Graves' disease,[2] 3% in Hashimoto's thyroiditis, 6% in Euthyroid status. In about 5-10% of patients, vision loss can occur due to corneal decompensation or optic nerve decompression. Smoking is found to be an important risk factor in Thyroid eye disease.

Financial or Other, Competing Interest: None.
Submission 07-08-2016, Peer Review 16-08-2016,
Acceptance 28-08-2016, Published 01-09-2016.
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DOI: 10.18410/jebmh/2016/814

MATERIALS & METHODS: All 30 patients presented with thyroid eye disease were subjected to detailed history taking, clinical examination, biochemical investigation and imaging. Accordingly, patients were categorised as mild, moderate and severe disease based on clinical activity score. Then, all patients are treated and followed at different intervals depending on the severity of disease.

Inclusion Criteria: All diagnosed cases of TED with following features of a) Lid signs b) soft tissue changes c) Restrictive myopathy[3] d) B/L Axial proptosis were included in this study.

Exclusion Criteria: Patients in chronic stable phase, inflammatory disorder other than thyroid disease were excluded from the study.

RESULTS: Mean age of presentation is 38.86%.

a) Age Distribution:

Age	No. of patients	%
20 -30 Years	10	33.33
31-40 years	8	26.66
41-50 years	8	26.66
51-60 years	4	13.33

Table 1: Shows age Distribution of Thyroid Patients Studied

b) Sex Distribution:

Male	12(40%)
Female	18(60%)

Table 2: Shows Sex Distribution of Thyroid Patients Studied

Male: Female ratio 1.5:1, this study also shows that males have more severe disease than females, 66.66% as compared to 33.33%, as smoking is an associated risk factor in male.

c) Thyroid Status:

Hypothyroid	1(3.33%)
Hyperthyroid	25(83.33%)
Euthyroid	4(13.33%)

Table 3: Shows Thyroid status of the Thyroid Patients Studied

d) Laterality:

Symmetrical (B/L)	21(70%)
Asymmetrical (B/L)	9(30%)

Table 4: Shows Laterality of Thyroid Patients Studied

e) Disease Severity Based on Symptoms & Signs:

Mild	50%
Moderate	30%
Severe	20%

Table 5: Shows Severity based on Symptoms and Signs of Thyroid Patients Studied

Clinical Manifestation:

Clinical features	No. of patients	Percentage (%)
Lid signs	30	100
Soft tissue infiltration 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 more than 4 mm	6	20
Proptosis more than 23 mm	6	20
Imaging with CT: EOM enlargement Fat enlargement	12 3	40 10
Smoking	9	30
Diabetes	2	6.66

Table 6: Shows Percentage Distribution of Risk Factor, Systemic Disorder, Various Clinical Manifestation, Differential IOP, Imaging among Thyroid Patients Studied

CT Orbit (Axial & Coronal View): CT Orbit was done for all patients. Extraocular muscle enlargement present in 40% patients and fat hypertrophy in 10% patients of patients and is more frequently seen in young individuals (Fig1a &1b).[1]

CT orbit showing muscle enlargement and fat hypertrophy:

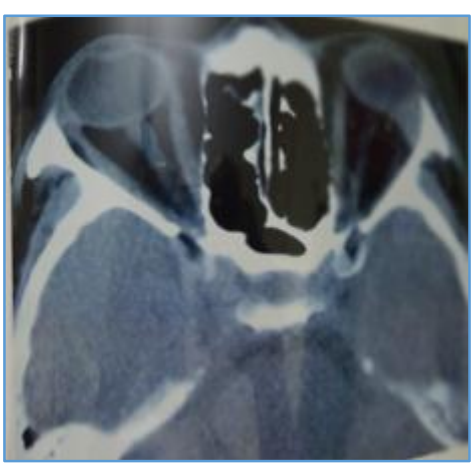

Fig. 1a: CT scan (Axial view) shows Muscle Enlargement with Relative of Tendons

Fig. 1b: CT scan (Coronal view) shows Muscle and Fat Enlargement Sparing

B-SCAN (7.5-10 MHz): It gave topographic information of extraocular muscle (Fig. 2).

A-SCAN: Tendon sparing muscle enlargement with corresponding low reflectivity was seen. (Fig. 3)

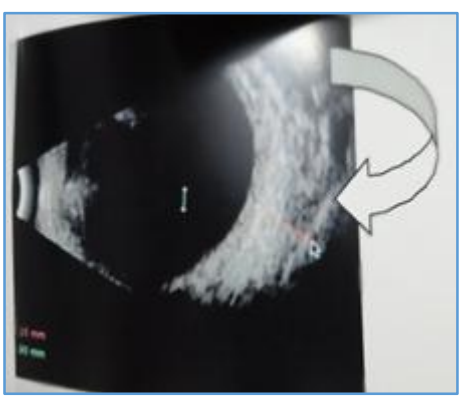

Fig. 2: Showing Tendon Sparing Muscle Enlargement in B-scan

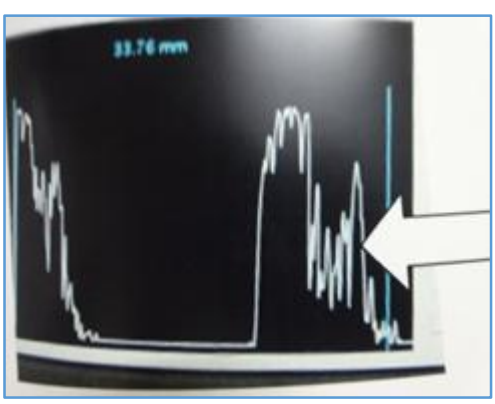

Fig. 3: Showing Low Reflectivity in A-scan

Biochemical Analysis: It Includes IL-6, HS-CRP, TFT. Serum levels of patients in moderate and severe stage were taken. IL-6 and HS-CRP done using ELISA in active phase (if CAS score more than 4) of moderate and severe disease and the results were compared with control group without thyroid eye disease (Table 7 and 8).

When the results are analysed, these parameters were found to be increased only in active phase of severe thyroid disease not significantly raised in moderate disease.

ANOVA Test - Interleukin-6:

Activity	No. of patients	Mean	Standard deviation	P value
Severe	6	102.53	150.58	0.013
Moderate	9	2.0311	26.81	
Control	18	15.43	.41	
Total	**33**	**27.61**	**72.42**	

Table 7

This test denotes significant at 5% level.

Table 7 – shows mean, standard deviation, P value of Interleukin-6 in ANOVA test among control group, moderate and severe active thyroid eye disease patients.

ANOVA Test –HS-CRP:

Activity	No. of patients	Mean	Standard deviation	P value
Severe	6	4.92	4.690	0.041
Moderate	9	3.34	3.22	
Control	18	1.77	.85	
Total	**33**	**2.77**	**2.81**	

Table 8

This test denotes significant at 5% level.

Table 8 – shows mean, standard deviation, P value of HS-CRP in ANOVA test among control group, moderate and severe active thyroid eye disease patients.

Response to treatment	No. of patients
Remission	26(86.66%)
Exacerbation	4(13.33%)

Table 9: Shows Remission and Exacerbation among Thyroid Patients Studied

Parameters Assessed during followup: Symptoms, lid signs, proptosis, diplopia, visual acuity, fields, colour vision, blood pressure, Hertel's exophthalmometry, random blood sugar, systemic side effects of steroids.

DISCUSSION: Thyroid Eye Disease also known as Grave's ophthalmopathy is an autoimmune inflammatory disorder usually associated with dysthyroid status. Approximately, 90% have Graves' hyperthyroidism, 1% have primary hypothyroidism, 3% have Hashimoto thyroiditis and 6% are euthyroid status. It is 5 times more common in women than in men except in old age group where the female: male ratio decreases. Smokers are up to seven times more likely to develop TED than non-smokers. It is frequently

asymmetrical. Disease process is severe in acute onset and in older age group.

Pathogenesis: Orbital fibroblast with CD-40 receptor when engaged by T-cell –bound CD-154 leads to proinflammatory cytokines are upregulated (IL-6, IL-8 &PGE2) leading to synthesis of hyaluronan and glycosaminoglycans, thus leading to increase in orbital volume and fat volume, inflammation, oedema, muscle injury and scarring. Also enhanced signalling through TSH–R on orbital fibroblast may promote adipogenesis especially in younger individual. Extraocular muscles and soft tissue swelling occurs secondary to infiltration by T-lymphocytes, macrophages, B-lymphocytes, plasma cells and mast cells along with deposition of GAG leading to EOM restriction, mass effect (proptosis, scarring) and compressive optic neuropathy[1,2.4].

Classification & Categorisation:
Mild Disease: Lid Lag, lid retraction, lagophthalmos and mild proptosis (Fig. 4). Most common in adult onset.

Moderate Disease: Persistent lid retraction[5], lid lag, moderate proptosis, some soft tissue change with swelling and intermittent myopathy that has an active course (Fig. 5).

Severe Disease: More inflammatory, cicatricial and mass effects (Fig 7) such as progressive Exophthalmos associated with significant soft tissue changes, myopathy, orbital apex syndrome with optic neuropathy.

Active Disease: Active disease implies the presence of inflammatory features and suggests the potential to respond to anti-inflammatory treatments.

Inactive Disease: Inactive disease implies no inflammation, yet residual fibrosis and secondary effects persist. In inactive disease, only surgical treatment can alter the outcome[4].

Clinical Features: Proptosis with lid retraction is the common presentation. Lid signs include Lid lag, lid retraction, mild thyroid eye disease, moderately active disease, moderately inactive disease.

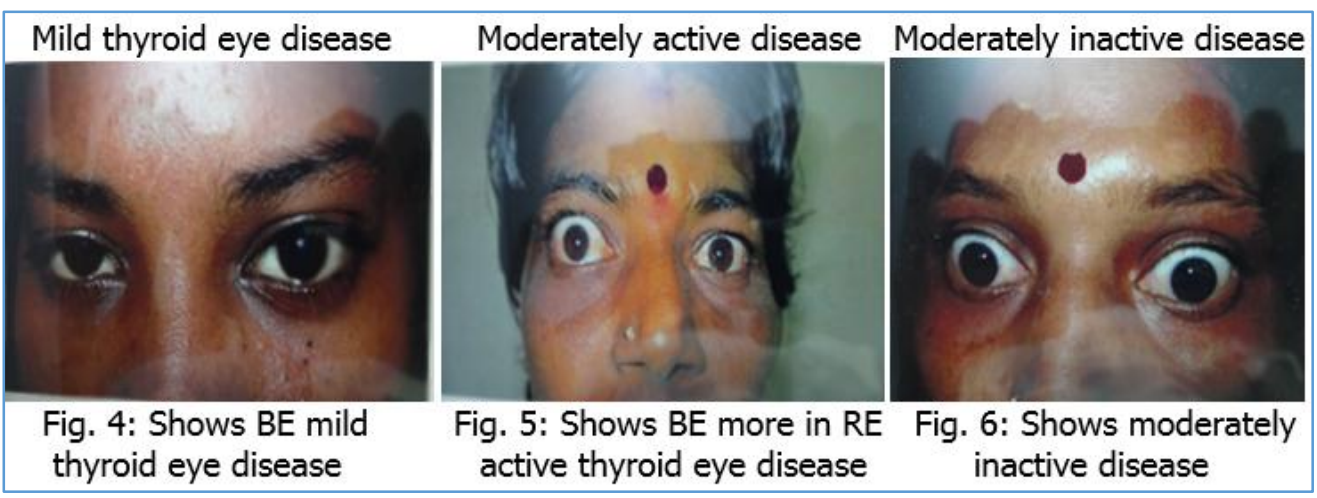

Fig. 4: Shows BE mild thyroid eye disease

Fig. 5: Shows BE more in RE active thyroid eye disease

Fig. 6: Shows moderately inactive disease

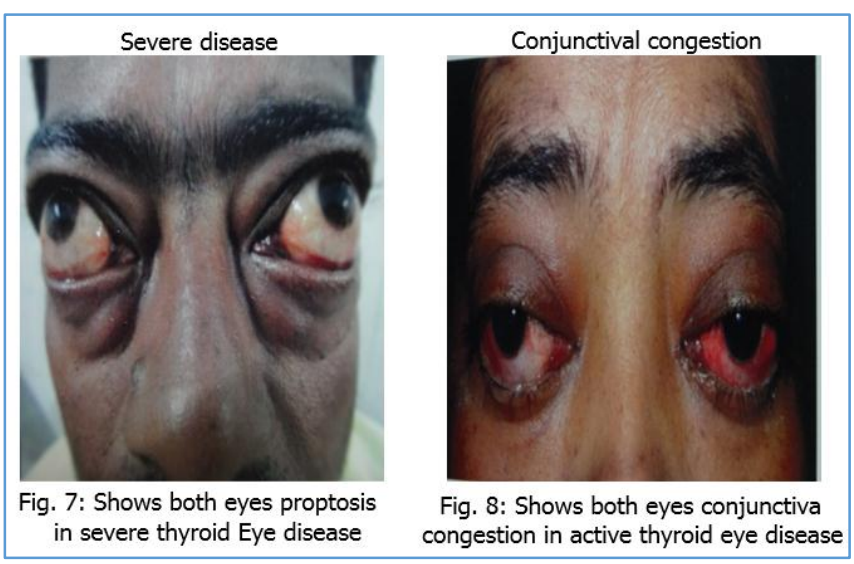

Fig. 7: Shows both eyes proptosis in severe thyroid Eye disease

Fig. 8: Shows both eyes conjunctiva congestion in active thyroid eye disease

Restriction of Extraocular Movements:

Fig. 9a: Showing restriction of Extraocular movements during Right dextroversion

Fig. 9b: Showing restriction of extraocular movements during elevation

Fig. 9c: Showing restriction of extraocular movements during depression

Soft Tissue Features: Tearing, lid oedema, conjunctival swelling, fat prolapse, when the orbit is more congested patient will complain of retrobulbar discomfort or something pushing behind the eye sometimes with lid oedema which worsens more in the morning.

Myopathic Feature: Diplopia with limitation of extraocular movement classically intermittent in onset, progressive in severe disease, inability to read for a long time, blurring on saccadic movement.

Patients with significant restriction of movement in all positions of gaze are at risk of developing optic neuropathy (Fig. 9a, b, c).

Dysthyroid Optic Neuropathy: This is more common in elderly male smokers with diabetes. It causes poor vision, colour vision, fields, RAPD, resistance to retropulsion, greater restriction of EOM, IOP increase in upgaze.

Interleukin 6: Interleukin 6 is a proinflammatory cytokine[5] secreted by the macrophages, T-cells and also by the adipocytes. It is encoded by IL-6 gene. IL-6 level increases in response to infection, inflammatory condition, which in turn stimulates acute phase reactants especially C-reactive protein.[6] IL-6 is implicated in the pathogenesis of many autoimmune disease especially thyroid eye disease. In thyroid eye disease, high levels of CD40 is found in the orbital fibroblast. Activation of CD40 by engagement with CD40L results in production of many cytokine especially IL6. This cytokine (IL6) is found to be detected in Thyroid tissue, extraocular muscles and Orbital fat of Thyroid disease patients.[7]

Highly sensitive C-reactive protein: C–reactive protein is an acute phase reactant secreted by liver cells in response to acute and chronic inflammatory conditions like Thyroid eye disease. Its secretion is increased in response to many cytokine especially IL-6.[8] HS–CRP measures low levels of CRP using laser nephelometry. CRP level is determined by their rate of production, they began to rise within one hour of inflammation during which even ESR remains negative. CRP[9] has prognostic value in inflammatory disorder as their value falls rapidly in response to therapy. CRP[10] is not routinely done to screen thyroid eye disease because they are highly non-specific and their levels are elevated in many other inflammatory disorder.

Management: All patients are advised to stop smoking to prevent the progression. Blood sugar should be under control. Then patient is treated according to the severity of the disease. Dysthyroid status should be corrected by drugs to maintain Euthyroid state. For mild disease, patients are treated with simple conservative measures like elevation of head of the patient to reduce periorbital oedema, lubricants and followed every 6 months. For moderate disease, dark goggles/gel pads to protect the cornea, prism glasses or selective ocular patching to relieve diplopia, oral steroids 1 mg/kg is given and the response for treatment then assessed after 2 weeks. For severe disease, pulse therapy of IV methylprednisolone 1 g daily given and the response assessed after 48 hours if there is a response, then switch over to oral steroids and followed weekly, otherwise orbital decompression is done for compressive neuropathy.

Glucocorticoid reduces inflammatory process and also controls retrobulbar fibrovascular proliferation and alleviates the symptoms and progression. Orbital radiation (20 Gray in 10 fractions) is indicated for rapidly progressive severe orbitopathy, it produces rapid relief in reducing the congestion and enhancing extraocular muscle function and relieves soft tissue changes in 4-6 weeks, but proptosis and ophthalmoplegia has very little response. It should be avoided in younger patients.

Surgical Management: Orbital decompression should be combined with aggressive anti-inflammatory therapy to minimise the effect of surgical trauma.

CONCLUSION: Though IL-6 and HS-CRP[10] is statistically significant in active severe disease, the role of these investigation in moderate disease could not be assessed. IL-6 is ELISA based analysis which is expensive and needs trained personnel to perform the procedure. So it could not be routinely done to screen for the activity of disease. Thus, clinical assessment remains the keystone in diagnosing disease activity in thyroid eye disease.

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