

Original Research Article

Association of level of IL-6, IL-10, IL-18, tumour necrosis factor- α with rheumatic mitral stenosis and subsequent pulmonary hypertension

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ABSTRACT

Background: Objective of the study was to provide insight on the immune response in patients of rheumatic heart disease, mitral stenosis and evaluation of various cytokines in pulmonary hypertension secondary to rheumatic heart disease.

Methods: Total 163 subjects, more than 18 year of age, were enrolled in this study. 84 subjects with rheumatic mitral stenosis (group A) diagnosed on two-dimensional echocardiography (2D echo) and 79 normal healthy volunteers (group B). Patients with mitral stenosis were further divided into subgroups based on severity of mitral stenosis [mitral valve area (MVA) >1 cm² and MVA ≤ 1 cm²] (subgroup Aa and Ab) and presence or absence of pulmonary hypertension [pulmonary arterial systolic pressure (PASP) ≥ 36 mm Hg] (subgroup Ac and Ad). Interleukins IL-6, IL-10, IL-18, tumour necrosis factor alpha (TNF- α) and high-sensitivity C-reactive protein (hs-CRP) levels were assessed in both groups.

Results: Mean IL-6, IL-10, IL-18, TNF- α and hs-CRP in group A and group B was 6.57 ± 3.53 and 2.73 ± 1 ($p \leq 0.001$), 8.185 ± 2.8 and 3.51 ± 0.86 ($p \leq 0.001$), 136.31 ± 89.0 and 47.96 ± 9.76 ($p \leq 0.001$), 21.26 ± 18.59 and 5.36 ± 3.57 ($p \leq 0.001$), 4.69 ± 6.3 and 2.63 ± 2.22 ($p \leq 0.008$) respectively. On subgroup analysis mean TNF- α in subgroup Aa was 20.71 ± 16.84 , while in subgroup Ab was 7.56 ± 1.93 ($p \leq 0.001$). Mean IL-10 in subgroup Ac and Ad was 8.74 ± 3.29 and 7.47 ± 1.82 , respectively. Differences in levels of other cytokines in these subgroups were not found statistically significant.

Conclusions: This study finds increased IL-6, IL-10, IL-18, TNF- α and hs-CRP levels in subjects with rheumatic mitral stenosis. Subjects with severe mitral stenosis had increased TNF- α levels. Subjects of mitral stenosis having pulmonary hypertension had increased IL-10 levels.

Keywords: Rheumatic mitral stenosis, Interleukins, Pulmonary hypertension

INTRODUCTION

Rheumatic heart disease remains a major public health problem in many parts of the world.^{1,2} Globally, India contributes nearly 25%–50% of newly diagnosed cases, deaths, hospitalizations, and burden of rheumatic heart disease (RHD).¹ The alarming prevalence to 2.2/1000 population of RHD continues to be a serious health burden in developing countries like India.³ The pathogenesis of rheumatic fever (RF) involves a complex network of genetic, environmental, and immunological interactions.

Genetic factors predispose individuals to developing autoimmune reactions.⁴ Cytokines are protein molecules, which send a range of stimulatory, modulatory, or inhibitory signals to the various cells of the immune system. Studies indicate that the inflammatory response in acute RF on cardiac tissues is generated by antigenic mimicry of the protein M leading to an abundant infiltration of CD4⁺ T cells.^{4,5} This leads to production of inflammatory cytokines [e.g. tumour necrosis factor-alpha (TNF- α), interleukins (IL-2 and IL-10)], which have a decisive influence on the immune response of patients with

RF.^{5,6} Inhibition of both IL-12 and interferon gamma (IFN- γ) by IL-10 promotes development of Th2 type cytokine pattern. Conceivably, many studies conclude that there is a switching of Th1 to Th2 type cytokine response as the disease progresses.⁷ This kind of Th1-Th2 dichotomy remains an important functional division in the immune system. Inflammatory mechanisms may play an important role in the natural history of pulmonary hypertension in RHD with special emphasis on its severe type, along with atrial fibrillation in RHD. In this study, an effort has been made to understand the immune response in patients of rheumatic heart disease, mitral stenosis and evaluation of various cytokines in pulmonary hypertension secondary to rheumatic heart disease. It will provide directions regarding planning of future studies with the same or other cytokines.

METHODS

This cross-sectional study was conducted among patients attending Govind Ballabh Pant Institute of Post Graduate Medical Education and Research (GIPMER) out-patient department. Serum cytokine level was assessed in total 163 subjects.

Group A included subjects with rheumatic mitral stenosis (n=84) and group B included healthy volunteers (n=79).

Group A patients were divided into subgroups: subgroup Aa (n=59) and subgroup Ab (n=25) [subjects with mitral valve area (MVA) ≤ 1 cm² and MVA > 1 cm² respectively] and subgroup Ac (n=47) and Ad (n=37) (subjects with pulmonary arterial systolic pressure (PASP) ≥ 36 mmHg and PASP < 36 mmHg respectively).

Patients with RHD mitral stenosis of age > 18 years diagnosed on the basis of echocardiography were included in study. Patients having moderate to severe mitral regurgitation, more than mild aortic stenosis, more than mild aortic regurgitation, chronic kidney disease, congenital heart diseases, any autoimmune or inflammatory condition, patients on steroid therapy and pregnant and lactating mother were excluded from study.

All eligible subjects underwent detailed history and baseline clinical assessment to assess extent of their valvular disease. Echocardiography was performed in all subjects using transthoracic echocardiography (TTE). The severity of mitral stenosis with or without associated regurgitation, along with the severity of associated aortic valve disease if present, was assessed as per following American college of cardiology/American heart association guidelines. Left atrial (LA) size measured with M-mode. MVA measured with MVA 2-D planimetry and PHT method, lower among the two values noted as final MVA of the patient. Pulmonary arterial systolic pressure (PASP) calculated by adding right ventricular systolic pressure (RVSP), which itself being measured by tricuspid regurgitation jet (RVSP=4V²) and right atrial pressure (RAP). The right atrial pressure can be estimated from the

end-expiratory diameter and respiratory changes of the inferior vena cava (IVC) as follows: normal diameter (≤ 2 , 1 cm) and inspiratory collapse ($> 50\%$), and RAP 3 mmHg (range, 0-5 mmHg); dilated inferior vena cava (IVC) (≥ 2 , 1 cm) with reduced respiratory variation ($< 50\%$), and RAP 15 mmHg (range, 10-20 mmHg); dilated inferior vena cava (IVC) (≥ 2 , 1 cm) with reduced respiratory variation ($< 50\%$), and RAP 15 mmHg (range, 10-20 mmHg); and IVC diameter and respiratory variation unfitting the previous paradigm, without resolving hepatic flow pattern (absence of prevalent systolic or diastolic flow component) or tricuspid E/e' wave ratio, and RAP 8 mmHg (range, 5-10 mmHg).⁸

Baseline laboratory tests such as renal function and liver function was conducted in all patients. Blood collected (10 ml) from cases and controls. Collected samples were centrifuged at 3000 rpm for 5 minutes, 30 minutes after collecting blood samples. Serum separated and kept in deep freezer at -80 degrees Celsius, until further processing. Levels of IL-6, IL-10, IL-18 and TNF alpha were estimated by using enzyme-linked immunosorbent assay (ELISA) kits as per the manufacturer's guidelines (Diaclone, France). The absorbance was estimated on fully automated ELISA reader by Tecan, Switzerland. hs-CRP was estimated by immunoturbidimetry using commercially available kits from Roche diagnostics Roche on cobas c 501 auto analyzer (Manheim Germany).

Data were analyzed with the help of statistical package for the social sciences (SPSS) 17, mean and standard deviation were calculated for baseline, echocardiographic and laboratory parameters. IL-6, IL-10, IL-18, TNF- α and hs-CRP were compared between group and subgroup by using student t-test. Pearson correlation coefficient calculated between above mentioned variables.

RESULTS

Total of 163 patients were enrolled for study. Group A had 84 subjects of rheumatic mitral stenosis (male=22, female=62). Group B comprises of healthy volunteers had 79 subjects (male=49, female=30). Mean age of patients in Group A was 34.6 \pm 10.6, while in group B mean age was 33.42 \pm 6.34 (years). Mean serum glutamic-oxaloacetic transaminase (SGOT) of group A was 47.3 \pm 16.1, in group B it was 30.1 \pm 11.4 (unit/liter), mean serum glutamic pyruvic transaminase (SGPT) of group A was 49.7 \pm 15.6, in group B it was 30.6 \pm 13.7 (unit/liter). Mean serum creatinine in group A was 0.75 \pm 0.27, while in group B it was 0.68 \pm 0.18 (mg/dl). Mean blood urea in group A was 34.6 \pm 9.2, in group B it was 27.0 \pm 6.9 (mg/dl) (Table 1).

Echocardiographic parameters

Mean MVA in subgroup Aa (n=59) (lower between 2-D and PHT) was 0.8 \pm 0.18, while in subgroup Ab (n=25) was 1.3 \pm 0.017 mean PASP (RVSP+RAP) in group subgroup Ac (n=47) was 55.3 \pm 20 and in subgroup Ad (n=37) was 26.3 \pm 4.5. Other significant lesion (moderate to severe)

beside mitral stenosis was present in 6 cases, with 3 subjects having moderate MR, 2 having severe MR and 1 subject having severe aortic stenosis.

Cytokines and inflammatory marker analysis

Mean IL-6 in group A was 6.57 with standard deviation of 3.53. Whereas mean IL-6 in group B was 2.73 with standard deviation of 1.07. (CI=3.05 to 4.69), (p≤0.001). Mean IL-10 in group A was 8.185 and standard deviation was 2.8036. Mean IL-10 in group B was 3.513, with standard deviation of 0.8612. (CI=4.228 to 5.344) (p≤0.001). Mean IL-18 in group A was 136.21, with standard deviation of 89.06, while mean IL-18 in group B was 47.9, with standard deviation of 9.76 (CI=68.517 to 108.784) (p ≤0.001). Mean TNF-α in group A was 21.26, standard deviation was 18.59, while mean TNF-α in group B was 5.366 with standard deviation of 3.57 (CI=11.13 to 18.51) (p≤0.0001). Mean hs-CRP in both groups were 4.69±6.38 and 2.63±2.22 respectively (CI= 0.19 to 2.75) (p=0.008).

Subgroup analysis

Among group A subjects when subgroup comparison done mean IL-6 in subgroup Aa (subjects with MVA ≤1 cm²) mean IL-6 was 5.63±3.25, while in subgroup Ab (subjects with MVA >1 cm²) mean IL-6 was 6.90±3.57 (p=0.139). Mean IL-10 in subgroup Aa was 8.38±3.06, mean IL-10 in subgroup Ab was 7.72±2.04 (p=0.326). Mean TNF-α in subgroup Aa was 20.71±16.84, while in subgroup Ab it was 7.56±1.93 (p≤0.001). IL-18 in subgroup Aa and Ab was 146.35±103.84 and 112.28±22.79 respectively (p=0.20). hs-CRP in subgroup Aa was 3.72±3.43 and in subgroup Ab it was 4.27±5.81 (p=0.673). Mean IL-6 in subgroup Ac and Ad was 6.86±3.5 and 6.21 ±3.49 respectively (p=0.441). Mean IL-10 in subgroup Ac and Ad was 8.74±3.29 and 7.47±1.82, respectively (p=0.028). Mean TNF-α in subgroup Ac was 20.25±17.02, in subgroup Ad it was 22.91±20.68 (p=0.532). Mean IL-18 in subgroup Ac was 145.298±103.01, while mean IL-18 in subgroup Ad was 124.676±66.95 (p=0.295). Mean hs-CRP in subgroup Ac was 4.77±6.13, whereas hs-CRP in subgroup Ad was 4.66±6.85 (p=0.938).

Table 1: Baseline characteristics of cases and controls.

Parameters	Group A	Group B	P value
Number	84	79	
Sex			0.01
Male	22	49	
Female	62	30	
Age (years) [mean]	34.6±10.6	33.42±6.34	0.390
SGOT (unit/l) [mean]	47.3±16.1	30.1±11.4	<0.001
SGPT (unit/l) [mean]	49.7±15.6	30.6±13.7	<0.001
S. creatinine [mean]	0.75±0.27	0.68±0.18	0.067
B. urea	34.6±9.2	27.0±6.9	0.001

SGOT- Serum glutamic oxaloacetic transaminase, SGPT- serum glutamic pyruvic transaminase.

Table 2: Echocardiographic variables in two groups.

Parameter	Type	Mean	Standard deviation	P value
MVA (cm²)	Subgroup Aa (n= 59)	0.8	0.18	<0.0001
	Subgroup Ab (n= 25)	1.3	0.17	
PASP (mmHg)	Subgroup Ac (n= 47)	55.3	20.0	<0.0001
	Subgroup Ad (n=37)	26.3	4.5	
Mean gradient (mmHg)	Subgroup Aa	14.3	6.5	0.012
	Subgroup Ab	9.9	5.6	
Peak gradient (mmHg)	Subgroup Aa	21.6	7.5	0.021
	Subgroup Ab	17.9	6.5	
LA size (cm)	Subgroup Aa	4.47	0.4	0.18
	Subgroup Ab	2.38	0.6	

MVA-mitral valve area, PASP-pulmonary arterial systolic pressure, LA-left atrium.

Table 3: Cytokines in group A and B.

Parameter	Type	Mean	Standard deviation	Lower CI	Upper CI	P value
IL-6 (pg/ml)	Group A	6.57	3.53	3.05	4.69	<0.001
	Group B	2.739	1.0			

Continued.

Parameter	Type	Mean	Standard deviation	Lower CI	Upper CI	P value
IL-10 (pg/ml)	Group A	8.185	2.80	4.228	5.344	<0.001
	Group B	3.513	0.86			
IL-18 (pg/ml)	Group A	136.31	89.06	68.517	108.784	<0.001
	Group B	47.96	9.76			
TNF- α (pg/ml)	Group A	21.26	18.59	11.13	18.51	<0.0001
	Group B	5.366	3.57			
hsCRP (mg/l)	Group A	4.69	6.38	0.19	2.75	0.008
	Group B	2.63	2.22			

IL – Interleukin, TNF - Tumor necrosis factor, Hs CPR - high-sensitivity C-reactive protein.

Table 4: Cytokines distribution in various subgroup.

Parameter	IL-6	p	IL- 10	p	IL-18	p	TNF- α	p	Hs-CRP	P
Sub group Aa	5.63±3.25	0.139	8.38±3.06	0.326	146.35±103.84	0.20	20.71±16.84	<0.001	3.72±3.43	0.673
Sub group Ab	6.90±3.57		7.72±2.04		112.28±22.79		7.56±1.93		4.27±5.81	
Sub group Ac	6.86±3.5	0.441	8.74±3.29	0.028	145.298±103.01	0.295	20.25±17.02	0.532	4.77±6.13	0.938
Sub group Ad	6.21±3.49		7.47±1.82		124.676±66.95		22.91±20.68		4.66±6.85	

IL – Interleukin, TNF - Tumor necrosis factor, Hs CPR - high-sensitivity C-reactive protein.

DISCUSSION

Inflammatory response initiated by autoimmune reaction in rheumatic heart disease leads to release of various inflammatory cytokines and these cytokines modulate immune response by either up-regulating or down regulating proliferation, activation, inhibition, and differentiation of immune cells. Studies of different pro-inflammatory and anti-inflammatory cytokines released by heart infiltrating cells assure their role in pathophysiology of the disease.⁴⁻⁶ This study was designed to assess systemic level of IL-6, IL-10, IL-18, TNF- α along with hs-CRP in rheumatic mitral stenosis, and obtain insight on progression of mitral stenosis, pulmonary hypertension secondary to rheumatic mitral stenosis.

In our study we observed significantly higher level of IL-6 in patients of rheumatic mitral stenosis in compare to healthy controls. IL-6 is a known pleiotropic cytokine, which is involved in induction of B cell differentiation. In a study by Toor et al, among young RHD patients, the serum concentration of IL-6 was significantly high along with IL-10 and TNF- α . In ARF cases, IL-6 was in greater concentration as compared to TNF- α but in young RHD cases TNF-a concentration were much higher than IL-6.⁹ High IL-6 and TNF- α levels could be the key elements of post streptococcal infectious sequelae.

In a study by Serag et al, in pulmonary hypertension secondary to rheumatic heart disease IL-6 concentration was significantly higher in rheumatic patients than in the control subjects, but it showed an insignificant higher level in patients with severe PAH than in those without severe PAH, very much similar to our study.¹⁰

IL-10 levels were significantly higher in patients of rheumatic mitral stenosis, in comparison to healthy control. IL-10 is considered anti-inflammatory in nature and inhibits production of pro-inflammatory Th1 cytokines (IL-12 and IFN- γ). IL-10 may directly modify the B-cell repertoire by altering the regulation of B-cell bcl-2 expression.¹¹ IL-10 promotes cytotoxic T-cell differentiation and proliferation and it also acts as a chemo attractant for CD8+ T-cells. Also, IL-10 induces recruitment and cytotoxic activity of CD8+ cells and supports the growth of cytotoxic T-cell precursors.⁷ In a study of 35 Brazilian patients, by Leão et al, IL-10 concentration detected in RF/RHD patients was significantly higher as compared to healthy individuals.¹² In another study by Guilherme et al, IL-10 was produced by a large number of human infiltrating cells from valve and myocardium tissue which is probably related to inflammation of myocardium.¹³ IL-10 was further even more significantly raised in patients of PAH, in comparison to patients of RHD mitral stenosis not having PAH. Although proposed, but this is for the first time IL-10 has been conclusively linked with PAH, secondary to

rheumatic mitral stenosis, in the best of our knowledge. Th17 cells have also been reported to be significantly increased in rheumatic mitral valve disease patients. Despite our current understanding, the precise interplay between IL-10 and IL-17 during the early and chronic stages of RF/RHD has not been fully elucidated.

We have also observed a significantly higher level of TNF- α in patients of RHD mitral stenosis, in comparison to healthy controls. These levels were further increased significantly in patients of severe mitral stenosis in comparison to mild to moderate mitral stenosis. Th-1 cytokine like IFN- γ and TNF- α , scar the valve. The scarred tissue becomes neovascularized and the disease quiescently progresses. Later, neovascularization within scarred tissue allows continuation of valvular injury leading to end-stage disease or irreversible deformation of the valve in rheumatic disease. IFN- γ and IL-6 amplifies response to TNF- α in these cells. High TNF- α levels take over to initiate damage to the heart which progresses to the valve scars limiting their functional ability.⁹ Chen et al studied TNF- α and IL-10 relationship in RHD patients and demonstrated that there was a significantly direct relationship between the plasma levels of TNF- α and IL-10 in the atrial and peripheral blood. The imbalance between TNF- α and IL-10 might result in an inflammatory net effect and has been suggested to play a pathogenic role in clinical progression in some diseases. This study did not support the hypothesis that in patients with mitral stenosis, elevated soluble TNF- α concentration was only associated with hemodynamic abnormality rather than with inflammatory activity.¹⁴ In contrast Chang et al in their study have concluded that elevated TNF- α and IL-6 levels are associated with hemodynamic abnormality and CHF rather than with rheumatic activity.¹⁵

In our study there was a significantly increased level of IL-18 in patients of RHD mitral stenosis in comparison to healthy controls. IL-18 a member of IL-1 family, supposedly secreted from smooth muscle cells, and act in autocrine or paracrine manner to recruit other smooth muscle cells to cause proliferation. In our study there were no significant difference in intergroup analysis between severe mitral stenosis patients's versus mild to moderate mitral stenosis patients and patients with pulmonary hypertension versus patients with RHD MS with no PAH. But if we study Pearson correlation, IL-18 was positively correlated with other cytokines and PASP and negatively correlated with MVA, both in a strong manner.

Levels of hs-CRP were also assessed in the study, hs-CRP was significantly increased in patients of rheumatic mitral stenosis in comparison to healthy controls. In subgroup analysis hs-CRP levels were not increased in patients of severe MS, patients with PAH. Cytokines, due to their pleiotropy and redundancy forms a complex network and supposedly along with cellular immunity and other hemodynamic variables results into progression of rheumatic heart disease.

There is yet no specific treatment to prevent the progression of RHD. Primary prevention of acute RF consists of early diagnosis and treatment of group A streptococcal tonsillopharyngitis with penicillin. In patients with a prior episode of RF, secondary prevention is critically important, but the efficacy of secondary prevention is limited in prevention of RHD progression. For this reason, new strategies and therapies are needed to prevent the relapse of acute RF and the progression of RHD. Role of various cytokines in pathogenesis will help us to plan appropriate therapeutic strategies with cytokine antagonists and arrest the progressive damage to the valves in subjects of RHD.

Limitations

This study assessed cytokines level in only patients without BMV/MVR, pre and post procedure assessment is desirable to rule out any hemodynamic contribution to elevation of cytokines level.

CONCLUSION

Systemic level of IL-6, IL-10, IL-18, TNF- α and hs-CRP were significantly higher in patients of rheumatic mitral stenosis. Levels of TNF- α were even higher in patients of severe mitral stenosis in comparison to mild to moderate mitral stenosis and level of IL-10 were significantly higher in patients of PAH in comparison to rheumatic MS patients not having PAH.

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