Correlation of IL-6, IL-10, IL-18 and TNF-α Levels with Severity of Rheumatic Mitral Stenosis and Secondary Pulmonary Hypertension

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Introduction

Rheumatic heart disease (RHD) remains a major public health problem in many parts of the world with an estimated world-wide prevalence of 33 million patients, of which about one-third cases (13.2 million) occur in India.

The pathogenesis of acute rheumatic fever involves a complex network of genetic, environmental and immunological interactions.

The inflammatory response in acute rheumatic fever, on cardiac tissues is induced by antigenic mimicry of the streptococcal protein M leading to an abundant infiltration of CD4+ T cells.

This leads to production of inflammatory cytokines (e.g., TNF-α, IL-2, and IL-10), which potentiate the immune response in rheumatic fever.

Hypothesis

The severity of mitral stenosis in many RHD patients continues to progress despite absence of recurrent rheumatic fever.

To determine the role of inflammatory cytokines in progression of rheumatic valvular injury and its hemodynamic sequelae- pulmonary hypertension.

Aims and Objectives

To determine the serum levels of cytokines IL-6, IL-10, IL-18, TNF-α and hs-CRP in peripheral blood of patients with chronic isolated rheumatic mitral stenosis and compare it with controls.

To determine association of serum levels of IL-6, IL-10, IL-18, TNF-α and hs-CRP with severity of rheumatic mitral stenosis & pulmonary hypertension.

Methodology

Total subjects screened: 184

Rheumatic heart disease with mitral stenosis: 84 (Group A)

Age and gender matched controls: 79 (Group B)

Investigations done:

EGC
ECHOCARDIOGRAPHY
Routine blood investigations
Serum IL-6, IL-10, IL-18, TNF-α, hs-CRP levels

Baseline Characteristics of Study Subjects

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Group A</th>
<th>Group B</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>84</td>
<td>79</td>
<td></td>
</tr>
<tr>
<td>Gender: Male</td>
<td>22</td>
<td>31</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>62</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>34.6 ± 10.6</td>
<td>30.0 ± 4.9</td>
<td>NS</td>
</tr>
<tr>
<td>Hb (gm/dL)</td>
<td>12.8 ± 1.8</td>
<td>13.1 ± 1.6</td>
<td>NS</td>
</tr>
<tr>
<td>TLC (per mm3)</td>
<td>4424 ± 1202</td>
<td>4892 ± 1486</td>
<td>NS</td>
</tr>
<tr>
<td>ESR</td>
<td>14.6 ± 2.9</td>
<td>12.4 ± 1.9</td>
<td>NS</td>
</tr>
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Echocardiographic Parameters of RHD Mitral Stenosis Group A

- Left atrial diameter: 4.47 ± 0.52 cm
- Mitral valve area: 0.95 ± 0.28 cm²
- Peak transmitial gradient: 20.18 ± 7.56 mm Hg
- Mean transmitial gradient: 13.08 ± 6.57 mm Hg
- Right ventricular systolic pressure: 42.58 ± 20.88 mm Hg

Subgroups of Rheumatic Heart Disease Patients

Rheumatic heart disease with mitral stenosis, n=84 (Group A)

Severity of mitral stenosis

Presence or absence of pulmonary hypertension

Results

- Presence or absence of atrial fibrillation did not have any impact on cytokine levels.
- There was strong linear correlation between various cytokine levels.

Conclusions

- Chronic rheumatic mitral stenosis patients have increased IL-6, IL-10, IL-18, TNF-α and hs-CRP levels suggesting a continuous ongoing inflammatory activity even in clinically silent chronic phase.
- Further subjects having severe mitral stenosis had increased TNF-α levels in comparison to subjects with mild to moderate mitral stenosis suggesting its possible role in acceleration of rheumatic process.

Inclusion Criteria

- Age > 18 years
- Subjects with chronic rheumatic heart disease with mitral stenosis diagnosed on echocardiography

Exclusion Criteria

- Any evidence of clinical infection
- Moderate to severe mitral regurgitation/aortic stenosis or regurgitation
- ARF in last 6 months/any other CV disease or pulmonary disease
- Pregnancy and lactating mothers
- Any autoimmune or inflammatory condition/other significant illness

Screen failure: 12

Exclusion Criteria

- Many autoimmune or inflammatory conditions/pulmonary disease
- Severe mitral stenosis and compare it with controls
- Presence or absence of pulmonary hypertension

Graph 1: Serum levels of IL-6, IL-10 and hs-CRP in Group A and B

Graph 2: Serum levels of IL-18 and TNF-α in Group A and B

Graph 3: IL-6, IL-18, TNF-α, hs-CRP levels

Graph 4: IL-10 levels in various subgroups

Clinical implications

- Chronic rheumatic mitral stenosis patients have increased IL-6, IL-10, IL-18, TNF-α and hs-CRP levels suggesting a continuous ongoing inflammatory activity even in clinically silent chronic phase.
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