Endothelin-1 Gene Polymorphisms in Severe Pulmonary Hypertension associated with Rheumatic Mitral Stenosis
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Introduction
- Rheumatic heart disease results from damage to heart valves caused by a single or recurrent episodes of rheumatic fever. It is endemic in developing countries including India.
- It has a worldwide prevalence of 33 million, resulting in about 3.5 million deaths worldwide annually.
- Mitral valve is most commonly involved and pulmonary hypertension (WHO group II) is a common sequelae of rheumatic mitral valve disease.
- Endothelin-1 (EDN1) is a potent vasoconstrictor with mitogenic and angiogenic properties and has a crucial role in the pathophysiology of idiopathic pulmonary arterial hypertension (WHO group I).
- Studies have shown that genetics plays a major role in the pathogenesis of idiopathic pulmonary arterial hypertension (WHO group I) and formed the basis for drug therapy with Endothelin receptor antagonists.
- However, the influence of genetics on pulmonary hypertension associated with mitral valve disease (WHO group II) is yet to be determined.
- The genetic variants of EDN1 may be involved in the pathophysiology of pulmonary hypertension associated with rheumatic mitral stenosis, and hence we sought to study the role of endothelin-1 gene polymorphisms in its pathophysiology.

Methods
- A total of 246 subjects were enrolled in the study comprising of 2 groups:
  - Group A: 123 consecutive cases of Pulmonary Hypertension (PH) associated with isolated chronic rheumatic mitral stenosis
  - Group B: 123 age and sex matched healthy controls
- All patients were enrolled over a period of 2 years from outpatient department of G.B. Pant Institute of Postgraduate Medical Education and Research, New Delhi.
- Demographics, history, clinical exam and detailed echocardiography exam done.
- Blood was collected for hemogram, anti-streptolysin O titre (ASO), C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), endothelin levels (by ELISA) and anticoagulated blood sample for DNA analysis.
- DNA was extracted from peripheral blood leukocytes and genotyping was performed by PCR-RFLP (Polymerase Chain Reaction-Restriction Fragment Length Polymorphism). Allelic and genotypic frequencies estimated in patient and control groups by appropriate statistical tests.

Results
- The mean right ventricular systolic pressure was 70.26±24.11 mm Hg and mean pulmonary end diastolic pressure was 25.96±10.29 mm Hg suggesting severe pulmonary hypertension.
- Lys198Asn polymorphism: Genotype Lys/Lys was present in 19.5% in Group A and 31.7% in Group B (p=0.04), genotype Lys/Asn was present in 61% in Group A and 60.2% in Group B (p=1), genotype Asn/Asn was present in 19.5% in Group A and 8.1% in Group B (p=0.02).
- The frequency of Asn/Asn homozygous was significantly higher in Group A suggestive of association of Lys198Asn polymorphism with pulmonary hypertension associated with rheumatic mitral valve disease.

Conclusions
- Endothelin-1 gene polymorphisms appear to play a significant role in the pathophysiology of pulmonary hypertension associated with rheumatic mitral valve disease.

References