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P017

Endothelin-1 Gene Polymorphisms in Severe Pulmonary Hypertension Associated with Rheumatic Mitral Stenosis

Friday, October 11, 2019, 10:15 – 11:15 AM, 2:25 - 3:25 PM
Saturday, October 12, 2019, 10:00 – 11:00 AM, 2:15 - 3:15 PM

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Purpose

Rheumatic heart disease is endemic in developing countries with a worldwide prevalence of 33 million, resulting in about 3,50,000 deaths worldwide annually. The mitral valve is most commonly involved and pulmonary hypertension (WHO group II) is a common sequalae of rheumatic mitral valve disease. Studies show that genetics plays a major role in the pathogenesis of idiopathic pulmonary arterial hypertension (WHO group I) and formed the basis for drug therapy. Endothelin-1 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). 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 pathogenesis.

Methods

A total of 246 subjects were enrolled in the study comprising of 123 consecutive cases of pulmonary hypertension associated with isolated chronic rheumatic mitral stenosis (Group A) and 123 age and sex matched healthy controls (Group B) over a period of 2 years from outpatient department of G.B. Pant Institute of Postgraduate Medical Education and Research, New Delhi. Demographic data, medical history, clinical examination and detailed echocardiography examination was 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 were estimated in patient and control groups by appropriate statistical tests.

Results

The mean age in Group A and Group B was 34.2±9.9 years and 35.4±9.3 years (p=0.331) respectively, with female preponderance: 65% females in Group A and 61.8% in Group B. In Group A, all patients had severe mitral stenosis with mean mitral valve area 0.81±0.18 cm^2. The mean diastolic trans mitral gradient was 11.74±4.71 mm Hg. The mean right ventricular systolic pressure (RVSP) was 70.26±24.11 mm Hg and mean pulmonary end diastolic pressure was 25.96±10.29 mm Hg suggesting severe

pulmonary hypertension. We studied 2 Endothelin-1 gene (EDN1) gene polymorphisms, Lys198Asn polymorphism which is G to T transversion at location 5665 affecting 61st nucleotide of exon 5 of endothelin-1 gene on chromosome 6 and 3A/4A polymorphism is insertion/deletion polymorphism located at exon 1 of endothelin-1 gene on chromosome 6. 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 genotype was significantly higher in Group A which suggests association of Lys198Asn polymorphism with pulmonary hypertension associated with rheumatic mitral valve disease. 3A/4A polymorphism: Genotype 3A/3A was present in 2.4% in Group A and 8.9% in Group B (p=0.05), genotype 3A/4A was present in 68.3% in Group A and 64.2% in Group B (p=0.59), genotype 4A/4A was present in 29.3% in Group A and 27.6% in Group B (p=0.89) which shows no significant differences between both the groups. Endothelin levels were similar between the two groups.

Conclusions

Endothelin-1 gene polymorphism appears to play a significant role in the pathophysiology of pulmonary hypertension associated with rheumatic mitral valve disease. The vasoconstrictor and mitogenic effects of endothelin may result in development of pulmonary hypertension in predisposed patients with severe rheumatic mitral stenosis.