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Inflammatory and Cardio Hypertrophic Remodeling Biomarkers in Patients with Fabry Disease

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Abstract : In Fabry disease (FD), α-galactosidase A (α-Gal A) deficiency leads to the accumulation of globotriaosylceramide (Lyso-Gb3 and Gb3), triggering a pathologic cascade that causes the severity of organs damage. The heart is one of the several organs with high sensitivity to the α-Gal A deficiency. A subgroup of patients with significant residual of α-Gal A activity with primary cardiac involvement is occasionally referred to as “cardiac variant.” The cardiovascular complications are most frequently encountered, contributing substantially to morbidity, and are the leading cause of premature death in male and female patients with FD. The deposition of Lyso-Gb-3 and Gb-3 within the myocardium affects cardiac function with resultant progressive cardiovascular pathology. Gb-3 and Lyso-Gb-3 accumulation at the cellular level trigger a cascade of events leading to end-stage fibrosis. In the cardiac tissue, Lyso-Gb-3 deposition is associated with the increased release of inflammatory factors and transforming growth factors. Infiltration of lymphocytes and macrophages into endomyocardial tissue indicates that inflammation plays a significant role in cardiac damage. Moreover, accumulated data suggest that chronic inflammation leads to multisystemic FD pathology even under enzyme replacement therapy (ERT). NF-κB activation plays a subsequent role in the inflammatory response to cardiac dysfunction and advanced heart failure in the general population. TNFalpha/NF-κB signaling protects the myocardial evoking by ischemic preconditioning; however, this protective effect depends on the concentration of TNF-α. Thus, we hypothesize that TNF-α is a critical factor in determining the grade of cardio-pathology. Cardiac hypertrophy corresponds to the expansion of the coronary vasculature to maintain a sufficient supply of nutrients and oxygen. Coronary activation of angiogenesis and fibrosis plays a vital role in cardiac vascularization, hypertrophy, and tissue remodeling. We suggest that the interaction between the inflammatory pathways and cardiac vascularization is a bi-directional process controlled by secreted cytokines and growth factors. The co-coordination of these two processes has never been explored in FD. In a cohort of 40 patients with FD, biomarkers associated with inflammation and cardio hypertrophic remodeling were studied. FD patients were categorized into three groups based on LVmass/DSA, LVEF, and ECG abnormalities: FD with no cardio complication, FD with moderate cardio complication, and severe cardio complication. Serum levels of NF-kB, TNFalpha, Il-6, Il-2, MCP1, ING-gamma, VEGF, IGF-1, TGFβ, and FGF2 were quantified by enzyme-linked immunosorbent assays (ELISA). Among the biomarkers, MCP-1, INF-gamma, VEGF, TNF-alpha, and TGF-beta were elevated in FD patients. Some of these biomarkers also have the potential to correlate with cardio pathology in FD. Conclusion: The study provides information about the role of inflammatory pathways and biomarkers of cardio hypertrophic remodeling in FD patients. This study will also reveal the mechanisms that link intracellular accumulation of Lyso-GB-3 and Gb3 to the development of cardiomyopathy with myocardial thickening and resultant fibrosis.

Keywords : biomarkers, Fabry disease, inflammation, growth factors
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