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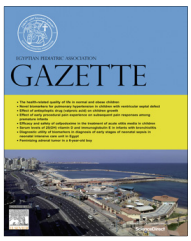

Novel biomarkers for pulmonary hypertension in children with ventricular septal defect

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KEYWORDS

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Abstract *Background:* Children with congenital heart disease (CHD) who have relevant systemic-to-pulmonary shunts will develop pulmonary hypertension (PH) if untreated. With advances in medical research, new biomarkers representing different physiological processes continue to emerge, providing an ever clearer risk profile for patients with PH.
Aim: To evaluate the role of serum galectin-3 and heart fatty acid binding protein (H-FABP) as early predictive biomarkers of PH in children with ventricular septal defect (VSD).
Method: The study included 50 children with VSD; 24 of them had PH and 25 age and sex matched healthy children serve as a control group. Serum levels of galectin-3, H-FABP and echocardiography evaluation were done for all cases and control subjects. We investigated the correlation between these markers and pulmonary pressure in children with VSD.
Results: Serum levels of galectin-3 and H-FABP were significantly higher in patients with PH. There was a significant positive correlation between both markers and pulmonary pressure. Galectin-3 and H-FABP have 76%, 60% sensitivity and 80%, 96% specificity respectively for prediction of PH in children with VSD.
Conclusion: Galectin-3 and H-FABP are promising cardiac biomarker for prediction and risk stratification of PH in children with VSD.

Introduction

Ventricular septal defect is one of the most common congenital heart diseases occurring in 50% of all children with congenital heart disease. The size of the VSD, the pressure in right and left ventricles, and pulmonary vascular resistance are factors that determine the hemodynamic changes in children with VSD.[1]

Left to right shunt through septal defect increases both blood pressure and flow through the pulmonary circulation, thus, in turn, induces irreversible changes of the medium-sized and small pulmonary arteries results in pulmonary

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obstructive arteriopathy, elevation of pulmonary vascular resistance (PVR) and reversal of shunt.[2] The minimum value of PVR increase remains controversial, especially in pediatric age group.[3] Prevention of this sequence of events is an important target in the management of septal defects, and may, in particular, motivate surgical intervention for closure of the defect. However, the clinical course of patients with septal defects is variable. In particular, it is not known how frequently PH develops and at which levels symptoms and irreversible changes will occur before closure of the defect.[4]

Pulmonary hypertension is a multifactorial and complex vascular disorder. Clinically, children with PH show various symptoms including shortness of breath, exercise intolerance, fatigue, respiratory symptoms and chest pain. Most of these symptoms are non-specific, and dependent upon age.[5] Without therapy, high PVR causes progressive right ventricular failure, low cardiac output, and high mortality. Current diagnostic methods include echocardiography, exercise testing and right heart catheterization.[6]

There is an emerging need for non-invasive and objective biomarkers to guide the diagnosis, treatment, and prognosis of PH in children. Currently, several biomarkers arising from sources related to ongoing processes of inflammation, coagulation, and ventricular strain have been identified in the pathophysiology of PH. However the multifactorial pathophysiology, variable clinical presentation, and association with other diseases make this a formidable challenge especially in pediatric age group.[7]

Galectin-3 is a soluble b-galactoside-binding lectin secreted by immune cells that regulate fibrogenesis, inflammation, cell proliferation, and tissue repair. Galectin-3 is involved in fibrosis in various organs, including the lung, liver, kidney, and heart through the promotion of macrophage migration, fibroblast proliferation and collagen synthesis.[8]

Heart type fatty acid-binding protein is a tissue specific cytoplasmic protein of small molecular weight (12–15 KD) that binds to long chain fatty acids and plays an important role in the intracellular utilization of fatty acids.[9] H-FABP is a sensitive marker for detecting latent ongoing myocardial damage and is a useful marker for detecting subjects at high risk for adverse cardiac events.[10] H-FABP can provide a dynamic view of the remodeling process and give information on the metabolic activity of cardiac muscles.[11]

In spite of the demonstrated role of galectin-3 and H-FABP for detection of cardiac impairment in several categories of patients with heart diseases, they are not widely studied for evaluation of pulmonary hypertension.

On the basis of these previous observations, we conducted the present study to determine whether galectin-3 and H-FABP, alone or in combination with clinical or echocardiographic findings, could reliably predict PH in children with VSD.

Patients and methods

This study is a cross sectional comparative study. It included all children with VSD confirmed by echocardiography who were referred to pediatric departments of Al-Azhar university hospitals (Al-Zahraa University Hospital, Al-Hussein University Hospital and Sayed Galal University Hospital), Cairo, Egypt during the period from July 2014 to March 2015. They were selected consecutively from both inpatients and outpatients who fulfill our inclusion criteria. Serum levels of galectin-3, H-FABP and echocardiography evaluation were done for all cases and control subjects. We investigated the correlation between these markers and pulmonary pressure in children with VSD. Informed consent was obtained from the participating parents in adherence to the guidelines of the ethics committee of Al-Azhar University, Cairo, Egypt.

Inclusion criteria include children with echocardiography confirmed VSD either with or without pulmonary hypertension, their age ranged between 6 months and 4 years.

Children with cyanotic heart disease, other structural heart disease than VSD, cardiomyopathy, heart failure, acute illness, non-cardiac systemic chronic diseases or those who underwent previous surgical correction were excluded from the study.

Based on our inclusion and exclusion criteria; the current study included 50 children with VSD; 24 of them had pulmonary hypertension. In addition, 25 healthy children serve as a control group. The control group was selected from age and sex matched healthy siblings of diseased children who had no structural heart disease confirmed by full history, examination, echocardiography and fulfill the same exclusion criteria for diseased group.

Clinical history and examination

All the studied children were subjected to a full history and through clinical examination. Clinical history includes the demographic data, presenting symptoms, any previous surgery, and current medications. Full data were recorded regarding manifestation of pulmonary congestion, low cardiac output symptoms, acute or chronic heart failure and failure to thrive. The findings of systemic and cardiac examinations were recorded in details. Nutritional assessment was done through dietetic history and anthropometric measurement (weight and length for age, weight/height ratio, head circumference, mid-arm circumference), presence of pallor and signs of vitamins deficiency.

Echocardiography

Echocardiography was performed for all subjects in both supine and left lateral position using Philips HD7.XE system. All cases were examined using multiple transducers ranging from 3.5 to 7 MHZ. with simultaneous electrocardiographic recording to allow timing of flow. Uncooperative children were given chloral hydrate according to body weight (50–5 mg/kg). M-mode and 2D echocardiography was used to measure the diameter of cardiac champers. PH is defined as a mean pulmonary artery pressure equal to or greater than 25 mmHg.[12]

Laboratory investigations

Measurement of galectin-3 and H-FABP level

Samplings (blood samples). 3 ml of venous blood samples were drawn under complete aseptic condition (alcohol swab 70%) in BD vacutainers (plain gel separator vacutainer). The sample in plain gel separator vacutainers was placed in water bath at 37 °C for 20 min then centrifuged at 3000 rpm for 10 min. Serum was aspirated in 2 Eppendorfs, one for galectin-3 assay and the other for H-FABP assay; both were stored at −80 °C