Serum Heart-Type Fatty Acid Binding Protein as A Diagnostic and Prognostic Predictor of Adverse Outcome in Children with Congestive Heart Failure

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Abstract

Background: Pediatric heart failure (HF) is a clinical and pathophysiological illness brought on by ventricular dysfunction, volume or pressure overload, either singularly or in combination. **Aim of study:** To estimate serum level of H-FABP before and after treatment of congestive heart failure, and correlate its level with severity of the disease. **Patients and methods:** This is a cohort case control research that was carried out in the cardiology unit of the pediatric department of Zagazig university hospitals between January 2018 and December 2018. (January 2019). This study included 54 children, who were divided into two groups: group (1), which comprised (27) children with CHF, and group (2), which included (27) children with no major history of any cardiovascular or systemic disorders. **Results:** In cases, HFABP levels were significantly higher than in the control group. There was also a significant difference in blood H-FABP levels in our patients before and after treatment (5.6 5.6 ng/ml vs. 2.1 0.61 ng/ml). **Conclusion:** In children with heart failure, H-FABP may be used as a diagnostic and prognostic indicator of poor outcome.

Key Words: Heart failure (HF), Heart-type fatty acid-binding protein (H-FABP), Serum level.

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The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Introduction

Heart failure (HF) is a clinical condition in which the heart is unable to pump enough blood to meet the metabolic demands of the body (1).

It is a clinical syndrome caused by cardiac structural and functional defects that impede ventricular filling or blood ejection. The most common cause of HF is decreased left ventricular myocardial function, but other probable reasons include dysfunction of the pericardium, myocardium, endocardium, heart valves, or great vessels alone or in combination. Some of the main pathogenic mechanisms causing HF are increased hemodynamic overload, ischemia-related dysfunction, ventricular remodelling, excessive neuro-humoral stimulation, abnormal myocyte calcium cycling, excessive or insufficient extracellular matrix proliferation, accelerated apoptosis, and genetic mutations (2).

Paediatric heart failure is a major cause of morbidity and mortality in children. Congenital heart disease and cardiomyopathies are the most common causes of cardiac failure in children. The principal causes of HF at birth are fetal cardiomyopathies or other heart abnormalities (such as sepsis, hypoglycemia, and hypocalcaemia). Severe aortic stenosis/aortic coarctation, hypoplastic left heart syndrome, and other diseases in which the ductus arteriosus closes substantially limit end-organ perfusion are the leading causes of CHDs with ductus-dependent systemic circulation in the first week after birth. CHDs with left to right shunts (such as ventricular septal defects, patent ductus arteriosus, and aortopulmonary windows) are typical causes of PHF in the first month of life because they cause pulmonary blood flow to rise steadily as pulmonary resistance decreases. Finally, HF in teenagers is primarily caused by cardiomyopathies or myocarditis rather than being related to CHDs (3).

A new biomarker known as heart type fatty acid binding protein has been shown to be secreted from the injured myocardium within an hour of the onset of ischemia (4).

It is also one of the prospective novel biomarker proteins since it is widely expressed in tissues with active fatty acid metabolism, such as the heart (5).

According to preliminary studies of people with congestive heart failure, elevated plasma concentrations of H-FABP and cardiac troponins cTnT were linked to a worse prognosis and worsening ventricular function. H-FABP levels were higher in patients with more severe heart failure (NYHA classes 3 and 4), and they were significantly related to serum cTnT. In addition, the patient subgroup with the highest serum H-FABP levels had the highest rate of recurrent cardiac events. These findings, which have been replicated in other patient populations, suggest that H-FABP is a sensitive marker of moderate myocardial injury in patients with congestive heart failure (6).

However, no comprehensive explanation of the clinical importance of serum H-FABP levels in children and adolescents has been provided (7, 8).

As a result, the goal of this study was to look at H-FABP levels in the blood of pediatric CHF patients before and after treatment to understand its relevance to the pathophysiology of the disease and to assess its diagnostic and prognostic significance in pediatric CHF.

Patient and Methods

This is a cohort case control study conducted at the cardiology unit of pediatric department of Zagazig university hospitals during a period from (January 2018) to (January 2019). All study participants, or their parents or legal guardians, gave their written consent after receiving full information. The Zagazig University Faculty of Medicine's Ethics Committee gave the study the thumbs up. In this study, 54 kids were involved, and they were split into two groups.

Group 1: Patient group including (27) children who were admitted to the pediatric cardiology unit and diagnosed as CHF patients from their history, symptoms, signs, ECG, and electrocardiographic data due to CHD, or cardiomyopathy.

Group 2: Control group including (27) children who were attend the outpatient clinic of pediatric department, with no significant history of any cardio-vascular diseases or systemic diseases with normal physical cardiac examination, ECG, and echocardiography.

Pediatric patients (infants and children) with their age ranged from 2 months to 5 years, of both sexes and all patients presented with manifestations of CHF and diagnosed as CHF due to CHD or cardiomyopathy by echocardiography were included.

Patients with cardiac diseases other than CHD or Cardiomyopathy, (myocarditis, arrhythmia), with CHF due to renal failure, with CHF due to hepatic disease, CHF due to pulmonary diseases, and

patients with CHF due to any acute or chronic illness were excluded from the study.

Methods:

All patients included in this study were subjected to the following initially on the first day of admission: complete history taking through a standardized clinical cardiology sheet, general and local examination and according to history taken the patient were classified according to the symptom based on Modified Ross classification of heart failure (9).

All patients were also subjected plain X-ray chest and heart (postero-anterior view): Cardiothoracic ratio (CTR) was measured for assessment of cardiomegaly, electrocardiography (ECG) and transthoracic echocardiography (TTE): including M mode left ventricular end-diastolic diameter (LVEDD) and end-systolic diameter (LVESD), septal thickness (IVS) and posterior wall (PW) thickness, EF% and FS% are measured lso, CBC, CRP, kidney and liver function tests and serum heart-type fatty acid binding protein (H-FABP) were done.

Statistical analysis

In order to examine the data, SPSS was used (USA). Statistical information shown as mean SD. The Wilcoxon signed rank test was used for non-paired non-parametric data, the independent student t test for non-paired non-parametric data, and the paired student t test for non-paired non-parametric data. Chi square analysis was used to examine categorical data that were expressed as frequency and percentage. The best cut-off values were determined using ROC curve analysis, or receiver operating characteristic analysis. At P0.05, the level of significance will be determined.

Results

Table 1. Demographic data of the studied groups

		Groups		Independent t Test	
		CHF Patients (n=27)	Control (n=27)	t/X²	P value
Age (Months)	Mean ± SD	29.2 ± 15.5	35.9 ± 15.7	t =-1.5	0.12
	Range	9-60	10-60		
Weight (Kg)	Mean ± SD	10.6 ± 4.7	14.3 ± 3.19	t =-3.2	0.002*
	Range	5-22.5	8-19		
Length (M)	Mean ± SD	0.84 ± 0.1	0.93 ± 0.1	t =-3.2	0.002*
	Range	0.68-1.05	0.73-1.1		
BMI	Mean ± SD	14.2 ± 3.5	16.4 ± 1.15	t =-3.9	0.005*
	Range	9.4-22.3	14.4-19		
Gender Male	N	13 (48.1%)	12 (44.4%)	X²=0.07	0.78
Female	N	14 (51.9%)	15 (55.6%)		

This table showed that there was significant difference between both groups regarding weight, length and BMI that was lower in CHF cases than control group. While there was no significant difference regarding age and gender.

Table 2. Clinical data and presenting symptoms among the studied CHF patients

Clinical Data	CHF Patients (n= 27)			
	Present		Absent	
	N	%	N	%
Symptoms				
Dyspnea	27	100	0	0
Cough	17	62.9	10	37.1
Failure to thrive	8	29.6	19	70.3
Fever	9	33.3	18	66.6
Signs				
Tachycardia	27	100	0	0
Tachypnea	22	81.4	5	18.5
Cyanosis	1	3.7	26	96.2
Congested N.Veins	0	0	27	100
L.L.edema	0	0	27	100
Cardiomegaly	27	100	0	0
Hepatomegaly	27	100	0	0
Murmur	22	81.4	5	18.5
Basal crepitation	5	18.5	22	81.4

This table showed that the most common symptom and sign was dyspnea and tachycardia respectively while the least common symptom and sign was fever and basal crepitation respectively.

Table 3. ROSS classifications among the CHF patients before and after treatment.

		CHF Group (n=27)		Wilcoxon signed rank test	
		Before treatment	After treatment	Z	P value
ROSS	Mean ± SD	3.1 ± 0.8	1.6 ± 0.78	-4.3	<0.001*
	Range	2-4	1-3		
ROSS classification	Class I	0	13 (48%)	Fischer exact 0.0001*	
	Class II	7 (26%)	6 (22%)		
	Class III	10 (37%)	4 (17.5%)		
	Class IV	10 (37%)	4 (17.5%)		

This table showed that Ross classification was significantly decreased after treatment of CHF cases. Also, there was 37% of patients with class III and IV Ross classification decreased to 17.5% after treatment, 26% of patients with class II Ross classification decreased to 22% after treatment while there were no patients with class I Ross classification before treatment and they increased after treatment to reach 48%.

Table 4. Echocardiographic data among the studied groups.

		Groups		Independent t Test	
		Patients (n=27)	Control (n=27)	t	P value
EDV (mm)	Mean ± SD	54.5 ± 7.9	47.2 ± 6.8	3.6	<0.001*
	Range	36-69	34-57		
ESV (mm)	Mean ± SD	39.4 ± 6.1	30.5 ± 5.7	5.5	<0.001*
	Range	25-51	22-40		
EF (%)	Mean ± SD	44.2 ± 10.3	63.6 ± 6.3	-8.3	<0.001*
	Range	28-65	55-75		
FS (%)	Mean ± SD	23.7 ± 6.1	33.2 ± 6.1	-5.7	<0.001*
	Range	15-35	27-46		
E wave (m/s)	Mean ± SD	0.73 ± 0.13	0.71 ± 0.11	0.64	0.52
	Range	0.6-1	0.6-1		
A wave (m/s)	Mean ± SD	0.77 ± 0.21	0.65 ± 0.11	2.6	0.01*
	Range	0.5-1.1	0.5-0.8		
E/A Ratio	Mean ± SD	0.97 ± 0.16	1.09 ± 0.15	-2.7	0.005*
	Range	0.67-1.4	0.86-1.4		

This table showed that there was significant difference between both groups regarding EDV, ESV, A wave that was higher in cases than control group and significant difference regarding EF, FS and E/A ratio that was lower in cases than control group.

Table 5. Serum HFABP among the studied groups.

		Groups		Independent t Test	
		CHF Patients (n=27)	Control (n=27)	t	P value
Serum HFABP (ng/ml)	Mean ± SD	5.6 ± 5.6	1.6 ± 0.18	6.5	<0.001*
	Range	2.3-11.9	1.4-1.9		

This table showed that there was significant difference between both groups regarding Serum HFABP that was higher in cases than control group

Table 6: Serum HFABP among CHF patients before and after treatment.

		CHF Group (n=27)		Paired t test	
Serum HFABP (ng/ml)		Before treatment	After treatment	t	P value
	Mean ± SD	5.6 ± 5.6	2.1 ± 0.61	5.9	<0.001*
	Range	2.3-11.9	1.7-4.5		

This table showed that there was significant decrease in serum HFABP after treatment in CHF group.

Table (7): Diagnostic and prognostic power of serum HFABP among CHF patients before and after treatment.

Area	P	95% Confidence Interval		Cut off (Before treatment)	Sensitivity	Specificity
		Lower Bound	Upper Bound	Greater or equal		
1.000	<0.001*	0.000	1.000	2.1	100%	100%
AUC	P	95% Confidence Interval		Cut off (after treatment)	Sensitivity	Specificity
		Lower Bound	Upper Bound	Greater or equal		
0.857	0.000	0.757	.958	1.75	82%	73%

Before treatment, serum HFABP at cut-off value of greater or equal 2.1 ng/ml, the sensitivity of serum HFABP Specificity was 100% as a diagnostic predictor of myocardial damage in CHF, AUC was 1.00 with p value >0.001. While after treatment, serum HFABP at cut-off value of greater or equal 1.75 ng/ml, the sensitivity of serum HFABP in CHF was 82% as a predictive factor of myocardial injury specificity was 73%, AUC was 0.857 with p value 0.000.

Discussion

Our data revealed no significant differences in age or gender, but a significant difference in weight, length, and BMI, which was lower in CHF cases than in the control group.

In contrast to our study, **Zoair et al.** (7) found that the mean age of their patients was 24 months, whereas the mean age of their control group was 21 months. Males made up 50% of their cohort, and there was no significant difference in age or sex between the two groups. However, there was no significant difference in weight. According to **Hayabuchi et al.** (10) the recruited patients had a mean age of 8.58.2 years and were 55% male and 45% female.

Regarding clinical data and presenting symptoms among the CHF patients studied, the findings revealed that 100% of cases had dyspnea, tachycardia, cardiomegaly, and hepatomegaly, 81.4% had tachypnea and murmur, 62.9% had cough, 29.6% had failure to thrive, and 33.3% had fever, 18.5% had basal crepitation, and 3.7% had cyanosis, and none had congested neck veins

According to **Zoair et al.** (7), 100% of cases had dyspnea and tachycardia, hepatomegaly and cardiomegaly, 66.67% had a cough, 30% had failure to thrive, 23.3% had fever, 93.3% had tachypnea, 40% had cyanosis, 23.3% had basal crepitation, 13.3% had congested neck veins, 30% had lower limb edema, and 80%.

Amir et al. (11) reported that feeding difficulty was found in 90% of patients, dyspnea in 59.8% of patients, repeated chest infection was seen in 49.8%, failure to thrive in 69.9%, tachycardia in 83.3%, displaced apex beat in 59.8%, cardiomegaly in 90%, hepatomegaly in 43.1%.

Regarding Ross classification of CHF among the studied patients, the results demonstrated that class III Ross classification was present in 37.1% of cases, class III in also 37.1% and 25.8% of cases had class II Ross classification while none had class I Ross classification. The Ross classification was significantly decreased after treatment of CHF cases.

According to the Ross classification of heart failure, 50% of **Zoair et al** patients were admitted in stage 3 and 30% were admitted in stage 4, which is consistent with our findings. Unfortunately, one patient died three months later from a chest infection (diagnosed as Down syndrome with common atrioventricular canal). However, just 6.8% of their patients remained in stage 4 and 51.7% had Ross classifications that had dropped to stage 2. **Hayabuchi et al.** (10) determined that the bulk of them (80%) were in NYHA functional class I, while 16% and 4% were in classes II and III, respectively.

There was a significant difference between the two groups in terms of EDV, ESV, and A wave, which were higher in cases than the control group, and a significant difference in terms of EF, FS, and E/A ratio, which were lower in cases than the control group, indicating impaired systolic and diastolic function.

In keeping with our findings, **Zoair et al.** (7) discovered a significant difference in fraction shortening (FS) and ejection fraction (EF) between the two groups in the echocardiographic features of the patients upon admission (impaired left ventricular systolic function in patients). The diastolic function, as evaluated by the E/A ratio, did not differ between the two research groups. This discrepancy may be due to differences in age groups and inclusion criteria.

According to **Hayabuchi et al. (10)** arterial oxygen saturation was below 90% in 29 patients, and LVEF was lowered to less than 50% in 29 patients (21%). Compared to our patients, theirs had more severe cyanosis.

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Conclusion

In children with congestive heart failure, H-FABP may be used as a diagnostic and prognostic predictor of unfavorable outcomes.

Conflict of interest

The author(s) declare(s) that there is no conflict of interest.

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