Journal of Advances in Medicine and Medical Research

32(22): 34-42, 2020; Article no.JAMMR.62406
ISSN: 2456-8899
(Past name: British Journal of Medicine and Medical Research, Past ISSN: 2231-0614, NLM ID: 101570965)

Plasma Growth Differentiation Factor-15 as a Prognostic Biomarker in Children with Congestive Heart Failure

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Authors' contributions

This work was carried out in collaboration among all authors. Author AMK designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Authors SBEN and HAES managed the analyses of the study. Author AMZ managed the literature searches. All authors read and approved the final manuscript.

Article Information

DOI: 10.9734/JAMMR/2020/v32i2230703
Editor(s):
(1) Dr. Emin Umit Bagriacik, Gazi University, Turkey.
Reviewers:
(1) Mudasir Bashir Gugjoo, Sher-e-Kashmir University of Agricultural Sciences & Technology of Kashmir, India.
(2) M. Bhanu Sridhar, Gayatri Vidya Parishad (GVP) College of Engineering for Women, India.
Complete Peer review History: http://www.sdiarticle4.com/review-history/62406

Original Research Article

Received 25 August 2020
Accepted 31 October 2020
Published 23 November 2020

ABSTRACT

Aim and Objectives: This study aimed to evaluate the plasma levels of Growth Differentiation Factor-15 (GDF-15) in children with congestive heart failure, also to evaluate the diagnostic and prognostic value of this novel biomarker in pediatric congestive heart failure, by correlation of its levels with the clinical status and the echocardiographic data of these patients.
Subjects and Methods: This study was conducted on Thirty (30) children with congestive heart failure (CHF), Patients were selected from those admitted to Pediatric Cardiology Unit, Pediatric Department, Tanta University Hospital, from (August 2018-April 2020), and thirty (30) healthy children, matched for age and sex, were enrolled as a control group. All children in this study were subjected to Plain X-ray chest and heart: Cardiothoracic ratio (CTR) was measured, and Echocardiographic assessment: Doppler and Two-dimensional, M-mode Echocardiographic evaluation of these parameters and Plasma level of Growth Differentiation Factor-15 (GDF-15) was measured.

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Results: the results revealed that The best cutoff point of GDF-15 to differentiate between cases with CHF and control group was >446.5 ng/l with 93.33% sensitivity, 90% specificity, 90.3% PPV, 93.1% NPV and AUC was 0.992.
There was significant decrease of EF% and FS% (systolic dysfunction of LV) in patients with CHF as compared to control group.
There was statistically significant positive correlation between plasma level of GDF-15 and Ross clinical stage of CHF.
There was statistically significant negative correlation between GDF-15 and EF%, FS % by echocardiography.
Conclusion: Plasma levels of GDF-15 were elevated in children with CHF, and these levels were correlated to the Ross staging of CHF and echocardiographic assessment of LV function. Plasma levels of GDF-15 were elevated in patients with bad prognosis, denoting its prognostic value as a novel biomarker in pediatric CHF.

Keywords: Prognostic biomarkers; congestive heart failure; growth differentiation factor-15.

1. INTRODUCTION

Heart failure continues to be a major public health and economic burden worldwide because of its chronic and progressive course, which carries a significant morbidity and mortality risk [1].

Congestive heart failure (CHF) refers to a clinical state of systemic and pulmonary congestion resulting from inability of the heart to pump as much blood as required for the adequate metabolism of the body. The clinical picture of CHF results from a combination of relatively low output, and compensatory responses to increase it [2].

In systolic dysfunction, the stroke volume decreases, thereby reducing cardiac output, subsequently, the heart responds with compensatory mechanisms like increasing left ventricular volume or elasticity, increasing contractile state by activation of circulating catecholamines, or increasing filling or preload. Each compensatory mechanism is limited, so in an untreated patient, the heart fails, leading to manifestations of heart failure [3].

In children, the causes of heart failure are significantly different from adults and many cases are due to congenital malformations which usually result in high output cardiac failure [4].

Many of children with congenital heart diseases receive early surgical intervention and it has been estimated that the yearly incidence of heart failure as a result of congenital defects is between 1 and 2 per 1000 live births [5].

Measuring biomarkers in the blood can facilitate pediatric heart failure management, as they provide valuable information on disease diagnosis, severity, and prognosis [6]; such as B-type natriuretic peptide (BNP), N-terminal pro-B-type natriuretic peptide (NT-pro BNP) [7] and growth differentiation factor-15(GDF-15) [8].

Growth differentiation factor-15 (GDF-15) is a member of the transforming growth factor-β superfamily [9], with both anti-inflammatory and immunosuppressive properties [10].

The levels of GDF-15 are upregulated following acute injury to the heart, liver, kidney, and lung [11].

Patients with chronic heart failure and elevated GDF-15 have worse outcomes [12], and increases in GDF-15 over time in such patients were shown to be associated with worsening heart failure [13].

Elevated GDF-15 was also suggested, in one preliminary study of patients with advanced heart failure, to be predictive of mortality largely to the same degree as NT-pro-BNP, high-sensitivity C-reactive protein, galectin-3 or high-sensitivity cardiac troponin T (hs-cTnT) [14].

2. PATIENTS AND METHODS

This study was conducted on Thirty (30) children with congestive heart failure (CHF), Patients were selected from those admitted to Pediatric Cardiology Unit, Pediatric Department, Tanta University Hospital, from (August 2018-April 2020), and they were 16 males and 14 females, their ages ranged from 1 month to 24 months. Thirty (30) healthy children, matched for age and sex, were enrolled as a control group. They were 15 males and 15 females, their ages ranged from 4 months to 24 months.

2.1 The Inclusion Criteria Were

Children in the pediatric age with congestive heart failure (CHF).

2.2 The Exclusion Criteria Were

Neuromuscular mitochondrial disease, renal disease, hepatic disease, lung disease or cancer, diabetes mellitus, obesity and acute or chronic illness other than cardiac disease.

2.3 All Children in this Study Were Subjected to the Following

2.3.1 Complete history taking, thorough clinical examination

Including heart rate, signs of congestive heart failure, and complete local cardiac examination.

2.3.2 Investigations

2.3.2.1 Plain X-ray chest and heart

Cardiothoracic ratio (CTR) was measured for assessment of cardiomegaly, ECG: Using 3 channel 1000 apparatus, Echocardiographic assessment: Doppler and Two-dimensional, M-mode Echocardiographic evaluation of these parameters and Plasma level of Growth Differentiation Factor-15 (GDF-15): Samples were collected on EDTA as anticoagulant, and it is done by using a sandwich enzyme-linked immunosorbent assay test {ELISA}

2.4 Blood sampling

Two milliliter of random venous blood sample was collected from each subject by use of disposable sterilized plastic syringes. The needle of the syringes was then removed and each sample was allowed to pass gently along the wall of EDTA vacutainer tube labeled with the patient name. The blood was mixed gently and centrifuged for 20 min at 2000-3000 r.p.m for separation of plasma, which was stored at -20°C till the time of analysis of GDF-15.

2.5 Statistical Analysis of the Data

Data were fed to the computer and analyzed using IBM SPSS software package version 20.0. (Armonk, NY: IBM Corp) Qualitative data were described using number and percent. The Kolmogorov-Smirnov test was used to verify the normality of distribution. Quantitative data were described using range (minimum and maximum), mean, standard deviation and median. Significance of the obtained results was judged at the 5% level.

3. RESULTS

The study included 30 children with congestive heart failure and corresponding 30 healthy control children. There was no significant difference between the two groups as regard age and sex. There was significant increase of RR and HR in children with CHF as compared to control group ($p<0.05$). There was significant increase of CTR (by chest X-ray: Cardiomegaly) in children with CHF as compared to control group ($p<0.05$). There was significant decrease of EF% and FS% (systolic dysfunction of LV) in patients with CHF as compared to control group ($p<0.05$). There was no significant difference between the two groups regarding E wave, A wave and E/A ratio ($p>0.05$). Plasma GDF_15 level in children with CHF was (2304.4 ± 1893.4 ng/l), (range 430.1 – 9576.0 ng/l), whereas in the control group it was (240.5 ± 203.6 ng/l), (range 22.50 – 891.7 ng/l), with highly significant increase of plasma GDF-15 in children with CHF as compared to control group ($p<0.001$) Table 1.

VSD was the most prevalent diagnosis among children with congestive heart failure, whether isolated in 11 cases (36.7%) of the cases or combined with other conditions in 14 cases (46.7%). Regarding the clinical presentation of CHF, dyspnea was detected in 33.3% of cases, tachypnea in 33.3%, lower limb edema in 30%, cardiomegaly in 26.7%, palpable liver in 16.7%, and compensated heart failure in 16.7% of cases. Among the diseased group with CHF, most cases were in stage 4 (33.3%), (26.7%) in stage 3, (23.3%) in stage 2 and (16.7%) of them were in Ross stage 1 of CHF. In children with CHF, 43.3% of cases showed good prognosis, 10% of cases were re-admitted again, whereas 46.7% of cases died Table 2.

The best cutoff point of GDF-15 to differentiate between cases with CHF and control group was >446.5 ng/l with 93.33% sensitivity, 90% specificity, 90.3% PPV, 93.1% NPV and AUC was 0.992 Table 3.

There was statistically significant positive correlation between plasma level of GDF-15 and Ross clinical stage of CHF. There was statistically significant negative correlation between GDF-15 and EF%, FS % ($p<0.05$). There was no significant correlation between GDF-15 level and E/A ratio ($p>0.05$) Table 4.

There was statistically significant increase in the plasma level of GDF-15 according to Ross stage of CHF ($p<0.05$). There was significant increase in plasma level of GDF-15 in patients who died more than those who were readmitted more than those with good prognosis ($p<0.05$) Table 5.

Table 1. Comparison between the two studied groups according to different parameters

	CHF (n = 30)	Control (n = 30)	Test of Sig.	p
Sex				
Male	16 (53.3%)	15 (50%)	χ^2=	0.796
Female	14 (46.7%)	15 (50%)	0.067	
Age (month)				
Mean ± SD.	8 ± 6.4	9.2 ± 4.8	U=	0.086
Median (Min. – Max.)	6 (1 – 24)	8.5 (4 – 24)	334.50	
Weight (kg)				
Mean ± SD.	6.2 ± 3.1	8.8 ± 3.2	U=	0.003*
Median (Min. – Max.)	6 (2.5 – 12)	9 (4 – 15)	249.0*	
Respiratory rate (cycles/min)				
Mean ± SD.	45.3 ± 5.2	34.3 ± 5.2	t =	<0.001*
Median (Min. – Max.)	45 (35 – 55)	33.5 (25 – 45)	8.180*	
Heart Rate (beats/min)				
Mean ± SD.	122.2 ± 8.8	107.9 ± 14.1	t=	<0.001*
Median (Min. – Max.)	120 (110 – 145)	107.5 (90 – 135)	4.741*	
CTR (by X-ray)				
Mean ± SD.	58.5 ± 4.9	50.5 ± 2.8	t=	<0.001*
Median (Min. – Max.)	58 (50 – 66)	50.5 (45 – 55)	7.787*	
EF (%)				
Mean ± SD.	42 ± 14.7	68.5 ± 2.3	t=	<0.001*
Min. – Max.	15 – 75	65 – 70	9.780*	
FS (%)				
Mean ± SD.	23.5 ± 9.19	35.4 ± 4.5	t=	<0.001*
Min. – Max.	14 – 40	28 – 43	6.357*	
E wave				
Mean ± SD.	0.8 ± 0.1	0.8 ± 0.1	t=	0.891
Min. – Max.	0.6 – 1	0.6 – 1	0.138	
A wave				
Mean ± SD.	0.7 ± 0.2	0.7 ± 0.2	t=	0.210
Min. – Max.	0.5 – 1	0.5 – 0.9	1.268	
E/A ratio				
Mean ± SD.	1.1 ± 0.3	1.2 ± 0.4	t=	0.264
Min. – Max.	0.7 – 1.6	0.7 – 2	1.129	
GDF-15(ng/l)				
Mean ± SD.	2304.4 ± 1893.4	240.5 ± 203.6	U=	<0.001*
Median (Min. – Max.)	1921.5(430.1 – 9576)	231.5 (22.5 – 891.7)	7.0	

*χ^2: Chi square test; t: Student t-test; U: Mann Whitney test; p: p value for comparing between the studied groups; *: Statistically significant at p ≤ 0.05*

Table 2. Distribution of the studied cases according to different parameters in CHF group (n = 30)

	No. (%)
Diagnosis	
VSD	6 (20%)
VSD, PH	5 (16.7%)
VSD, MR	2 (6.7%)
VSD, TR	1 (3.3%)
VSD, PDA	2 (6.7%)
VSD, MR, mild PH	2 (6.7%)
VSD, ASD	2 (6.7%)
VSD, MR, TR, mild PH	1 (3.3%)
TGA, VSD	2 (6.7%)
MR, PDA	1 (3.3%)
MR, moderate TR	2 (6.7%)
MR, TR, severe PH	1 (3.3%)
Large VSD, PDA, PH	1 (3.3%)
VSD, MR, AR	1 (3.3%)
Coarctation of aorta	1 (3.3%)
Clinical presentation	
Tachypnea	10 (33.3%)
Dyspnea	10 (33.3%)
Lower limb edema	9 (30%)
Cardiomegaly	8 (26.7%)
Hepatomegaly	5 (16.7%)
Compensated HF	5 (16.7%)
Clinical Ross stage	
Stage 1	5 (16.7%)
Stage 2	7 (23.3%)
Stage 3	8 (26.7%)
Stage 4	10 (33.3%)
Prognosis	
Good	13 (43.3)
Readmission	3 (10%)
Died	14 (46.7%)

Table 3. ROC curve for GDF-15 to predict diseased cases with CHF

	AUC	P	95% C. I	Cut off	Sensitivity	Specificity	PPV	NPV
GDF-15 (ng/l)	0.992	<0.001*	0.979–1.006	>446.5	93.33	90.0	90.3	93.1

*AUC: Area Under a Curve; p value: Probability value; CI: Confidence Intervals; NPV: Negative predictive value; PPV: Positive predictive value; *: Statistically significant at p ≤ 0.05*

Table 4. Correlation between GDF-15 and variable clinical and echocardiographic data in children with CHF

	GDF15	
	r_s	p
Clinical stage (Ross)	0.660	<0.001*
EF %	– 0.715	<0.001*
FS %	-0.486	0.015*
E/A ratio	0.123	0.548

*r_s: Spearman coefficient; *: Statistically significant at p ≤ 0.05*

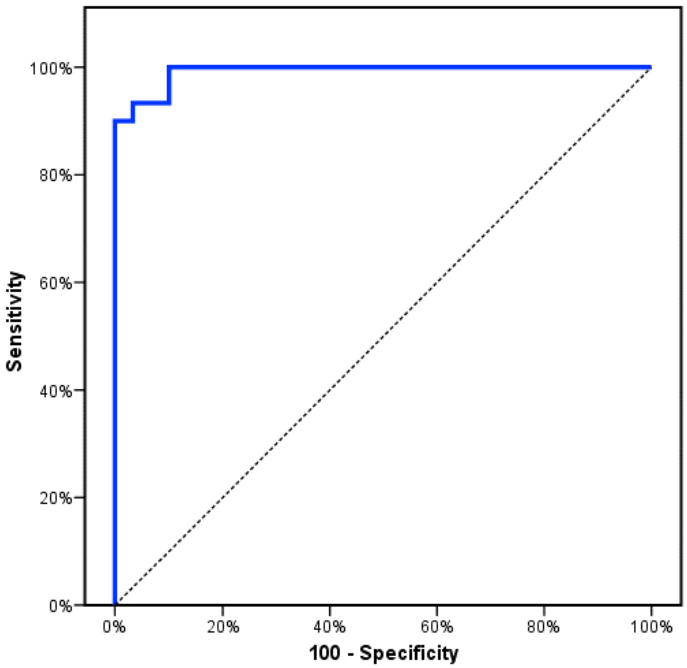

Fig. 1. ROC curve for GDF-15 to predict diseased cases with CHF

Table 5. Relation between GDF-15 with ross clinical stage and prognosis in children with CHF

	N	GDF-15(ng/l)			H	p
		Min. – Max.	Mean ± SD.	Median		
Ross clinical stage						
1	5	596.6 – 1955.4	1183.6 ± 491.1	1155.6	15.151*	0.002*
2	7	430.1 – 1396.6	991.9 ± 395	1121.4		
3	8	1155.3 – 3637.6	2460.8 ± 836.1	2339.8		
4	10	955.3 – 9576	3658.4 ± 2588.6	2773		
Prognosis						
Good	13	446.5 – 2669	1360.6 ± 685.1	1155.6	15.943*	<0.001*
Readmission	3	430.1 – 4021.2	2401.4 ± 1821.2	2752.8		
Died	14	2067 – 9576	3867 ± 2019	3241.1		

*H: H for Kruskal Wallis test; p: p value for association between; GDF-15 and different parameters; *: Statistically significant at p ≤ 0.05*

4. DISCUSSION

Growth differentiation factor-15 (GDF-15) is a member of the transforming growth factor-b cytokine superfamily and was originally cloned from activated macrophages [8].

Recent studies suggested that high plasma GDF -15 levels are associated with an increased mortality in patients with acute coronary syndrome and acute heart failure [1].

The aim of this study was to evaluate the plasma levels of Growth Differentiation Factor-15 (GDF-15) in children with congestive heart failure, and to evaluate the prognostic value of this novel biomarker in pediatric CHF, by correlation of its levels with the clinical status and the echocardiographic data of these patients.

In this study, there was no significant difference in the mean age and sex between the two studied groups. The weight of children with CHF

was statistically significantly decreased as compared to control group.

This is in agreement with Azevedo et al. [15], Madriago and Silberbach (2010), who reported decreased body weight in children with CHF as infants and children with CHF have feeding problems, catabolic state and even cachexia. Von Haehling et al. [16], reported that in HF patients there is a state of catabolic- anabolic imbalance leading to weight loss. This could be explained by the state of malnutrition and repeated infections associated with complicated CHD [17].

As regard heart rate (HR) and respiratory rate (RR), the present study showed that there was significant increase of HR and RR in patients with CHF as compared to control group.

This is in agreement with Erickson, [18], who reported that tachycardia and tachypnea in children with CHF occur due to sympathetic overstimulation and catecholamine release.

In this study, VSD was the most prevalent diagnosis among children with CHF whether isolated or combined with other conditions, as with PH, MR, or PDA. Also in this study, among the 30 children with CHF, 5 of them were in Ross stage 1, 7 in stage 2, 8 in stage 3 and 10 in stage 4 according to modified Ross classification. This is in agreement with the study of Li et al. [7].

As regard echocardiographic parameters in this study, there was significant decrease of EF% and FS% (systolic dysfunction of LV) in patients with CHF as compared to control group. There was no significant difference between both groups regarding E/A ratio (no diastolic dysfunction of LV).

This is in agreement with abou-raya et al. [19], who reported decreased LV systolic function (EF % and FS %) in patients with CHF as compared to control subjects.

On the other hand Banerjee et al., [20], reported decreased E/A ratio less than 1(LV diastolic dysfunction) in patients with CHF, this was in disagreement with our results which showed normal E/A ratio.

In the present study, there was highly significant increase of plasma GDF-15 in children with CHF as compared to control group ($p<0.001$).

This comes in agreement with Li et al., [21] ,who reported that the HF group in their study demonstrated higher levels of GDF-15 than the Non-HF group.

In the present study, there was statistically significant positive correlation between the level of GDF-15 and the Ross clinical stage of CHF, and significant negative correlation between the level of GDF-15 and EF % and FS %.

Nair and Gongora, [22] showed that GDF-15 correlated negatively with LVEF ($r = -0.49$, $p = 0.003$) and positively with LVIDd ($r = 0.5$, $p = 0.002$).

Kempf et al. [23] reported that patients with HF with reduced ejection fraction (HFrEF) have increased concentrations of GDF-15.

Our results are in disagreement with Li et al. [21], who reported no significant correlation between GDF-15 and LVEF.

In the current study, there was statistically significant increase in the plasma level of GDF-15 according to the Ross stage of CHF.

Li et al., [21], reported that plasma GDF-15 level was positively correlated with modified Ross score.

In our study, the best cutoff point of GDF-15 to differentiate between cases with CHF and control group was >446.5 ng/l with 93.33% sensitivity, 90% specificity, 90.3 PPV, 93.1% NPV and AUC was 0.992.

Li et al., [21], reported that according to ROC analysis, the AUC of GDF-15 for detection of HF was 0.757. Sensitivity and specificity was 68.8% and 71.2% respectively, for the cut-off value of 1306 ng/mL.

This study has some strength points as (to the best of our knowledge) no study has estimated the prognostic performance of GDF-15 in early detection of congestive heart failure in the age group of children with 2 years or less. GDF-15 was shown to be a sensitive and early non-invasive prognostic biomarker in prediction of pediatric CHF.

5. CONCLUSION

Plasma levels of GDF-15 were elevated in children with congestive heart failure (CHF), and

these levels were correlated to the Ross staging of CHF and echocardiographic assessment of LV function. Plasma levels of GDF-15 were elevated in patients with bad prognosis, denoting its prognostic value as a novel biomarker in pediatric CHF.

CONSENT AND ETHICAL APPROVAL

The study was approved by the Ethics Committee of Faculty of Medicine, Tanta University. Written informed consent was obtained from all parents or guardians of the included children.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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Peer-review history:
The peer review history for this paper can be accessed here:
http://www.sdiarticle4.com/review-history/62406