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Mid Regional Proadrenomedullin as a Diagnostic Marker in Pediatric Heart Failure

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ABSTRACT

Background: Heart failure remains an essential reason of morbidity and mortality in children. The measurement of various biomarkers might be worthy incentive in the diagnosis.

Objective: We studied the plasma level of MR-proADM as a promising novel diagnostic cardiac biomarker in pediatric patients with congestive heart failure and its relation to different clinical, laboratory and echocardiographic variables, aiming to promote their health through achieving good control of their cardiac symptoms and improving their quality of life.

Patients and methods: The present study included 80 subjects in the pediatric age from (6 months – 16 years). They were classified into two comparative groups: case group included 40 pediatric patients, well diagnosed as having congestive heart failure and control group included 40 apparently healthy pediatric subjects.

Results: There was an increase in MR-proADM level among cases group compared to control group and the difference was highly statistically significant.

Conclusion: We concluded that there was a high diagnostic value of measuring plasma level of MR-proADM at admission, regarding the diagnosis in the setting of pediatric congestive heart failure.

Keywords: Heart failure, MR-proADM, On-admission plasma levels.

INTRODUCTION

Heart failure (HF) is defined as a complex clinical disorder presented with ventricular dysfunction, insufficient peripheral blood flow and neuroendocrine activation **(1).** The spectrum of causes of heart failure is wide in pediatric patients noticing that congenital heart diseases (CHDs) represent the most common etiology. However, the clinical presentation of heart failure in infants and small children shows some peculiarities **(2).**

Comprehensive analysis of medical history, symptoms, biochemical tests and results of echocardiography are the corner stones for accurate diagnosis of heart failure. Circulating biomarkers may play a very important role in the diagnosis and management of patients presenting with heart failure and that allows better prognosis of the cases **(3).**

The cardiovascular system is regulated by various neurohumoral components, including the autonomic nervous system, renin–angiotensin–aldosterone system and various neuropeptide hormones **(4).**

Novel biomarkers typically reflect different components of the complex HF pathophysiology such as fibrotic remodeling, myocardial stretch or inflammation, and their complementary use has been shown to greatly enhance their prognostic and diagnostic power **(5).**

Natriuretic peptides, especially B-type natriuretic peptide (BNP) and its precursor N-terminal pro-B-type natriuretic peptide (NT-proBNP), are currently used in clinical practice and their measurement is recommended by the European Society of Cardiology (ESC) guidelines for the diagnosis and assessment of HF **(6).**

Despite their important role in HF, natriuretic peptides show some limitations. They are elevated in other conditions as well as HF, such as valvular heart disease, pulmonary hypertension, pulmonary thromboembolism, atrial fibrillation and sepsis. Age and kidney failure increase natriuretic peptide levels, while obesity is associated with lower levels. These situations can give values in a gray area that requires particularly careful analysis. The investigation of new biomarkers that can complement natriuretic peptides has been the subject of considerable attention**.** Adrenomedullin (ADM) is a 52 amino-acid peptide that belongs to the calcitonin family. Initially isolated from the adrenal gland, has diverse physiological and pathophysiological functions in the cardiovascular system. It is produced in many organs and tissues including the vasculature. ADM has numerous actions, including vasodilation, natriuretic, antiapoptosis and stimulation of nitric oxide (NO) production. It might play a protective role in various cardiovascular pathologies **(7).**

In HF, as a consequence of pressure/volume overload and ventricular wall stretching, the ADM gene is upregulated in cardiac myocytes.

The resulting high ADM levels appear to have a protective effect in the myocardium, as they lead to a decrease in preload and after load. Some studies suggest that ADM additionally inhibits cell growth and hypertrophy; it has also been associated with reductions in remodeling and fibrosis. Clinical use of ADM was limited for some time because of the in vitro instability of this biomarker: its half-life is short and it is quickly removed from the circulation. This problem was solved by the use of mid regional proadrenomedullin (MR-proADM), a stable fragment of pro-ADM whose concentrations reflect those of ADM **(8).**

We studied the plasma level of MR-proADM as a promising novel diagnostic cardiac biomarker in pediatric patients with congestive heart failure and its relation to different clinical, laboratory and echocardiographic variables, aiming to promote their

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health through achieving good control of their cardiac symptoms and improving their quality of life.

PATIENT AND METHODS

This descriptive study was conducted in the Pediatric ICU and Pediatric Cardiology Unit, Pediatric Department, Zagazig University Hospitals during the period between September 2021 and February 2022.
The present study included 80 subjects in the pediatric age from (6 months – 16 years). They were classified into two comparative groups:

I-Study group: It included 40 pediatric patients, well diagnosed as having congestive heart failure and selected randomly through systematic sampling technique from patient admitted to Pediatric Cardiology Unit and Pediatric Intensive Care Unit at Zagazig University Hospital and fulfilling the following inclusion and exclusion criteria:

Inclusion criteria:

Pediatric patients (6 months – 16 years), with congestive heart failure or dilated cardiomyopathy with reduced ejection fraction ≤ 50 % [9]. Male and female with a written consent from the parents or care giver.

Exclusion criteria:

Children with previous surgical cardiac correction. Patients with non-cardiac systemic chronic diseases. Drop outs and refusals.

II-Control group: It included 40 apparently healthy pediatric subjects, selected randomly from relatives and neighborhoods of study group and properly matched with them regarding age, sex and socioeconomic standard.

All the children included in the study were subjected to the following:

Comprehensive history taking, thorough clinical examination, laboratory investigations including:
complete blood count, CRP, serum Na, K, Ca and Mg and serum Pro-ADM.

Ethical considerations:

The study was approved by the Ethical Committee of the Faculty of Medicine, Zagazig University. Informed written consent was obtained from parents of all participant children before recruitment in the study, after explaining the objectives of the work. Confidentiality was guaranteed on handling the data base. This work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Statistical analysis

The collected data were coded, processed and analyzed using the SPSS (Statistical Package for the Social Sciences) version 22 for Windows® (IBM SPSS Inc, Chicago, IL, USA). Data were tested for normal distribution using the Shapiro Wilk test. Qualitative data were represented as frequencies and relative percentages.

Chi square test (χ^2) was used to calculate difference between two or more groups of qualitative variables. Quantitative data were expressed as mean ± Sd (Standard deviation), range, median, and interquartile rang (IQR). Independent samples t-test was used to compare between two independent groups of normally distributed variables (parametric data) and Mann-Whitney test was used for the nonparametric data. P value < 0.05 was considered significant.

RESULTS

There were no statistical significant differences between the studied groups as regard mean age or sex distribution (table 1).

Table (1): Demographic data of the studied groups

Variable		Cases (n=40)		Control (n=40)		MW	P
Age: (years)	Mean ± Sd	2.39±1.56		2.97±2.27		0.69	0.49
	Range	7 months -7 years		7 months -9 years			
	Median (IQR)	2(1.14-3)		2(1-3.5)			
Variable		**No**	**%**	**No**	**%**	χ^2	**P**
Sex:	Male	28	70	22	55	1.92	0.17
	Female	12	30	18	45		

Sd: Standard deviation, MW: Mann-Whitney test, χ^2: Chi square test

This table shows that the most frequent symptoms among the studied cases were cough and fever. Regarding Ross scoring class 47.5% were class IV, 10% were class III and 42.5% were class II.

Table (2): Clinical findings among the studied cases group

Variable	Cases (n=40)	
	No	%
Cough	38	95
Dyspnea	26	65
Cyanosis	26	65
Excessive sweating	20	50
Difficult feeding	26	65
Gallop rhythm	12	30
Hepatomegaly	8	20
Edema	14	35
Ascites	16	40
Fever	38	95
Ross scoring Class: II	17	42.5
III	4	10
IV	19	47.5

This table shows that there was a statistical significant increase in IVS and PW and statistical significant decrease in EF and FS among cases group compared to control group.

Table (3): Echo parameters among the studied groups

Variable		Cases (n=40)	Control (n=40)	t	P
LVEDD (mm)	Mean ± Sd	30±9.06	27.7±7.29	1.25	0.22
LVESD (mm)	Mean ± Sd	19.65±9.5	17.3±5.16	1.38	0.17
IVS (mm)	Mean ± Sd	6.58±1.75	6±0	**2.08**	**0.04***
PW (mm)	Mean ± Sd	6.41±1.74	5.57±0.94	**2.67**	**0.009****
EF (%)	Mean ± Sd	59±15.21	74.22±5.63	**5.93**	**<0.001****
FS (%)	Mean ± Sd	31.05±11.11	40.2±3.2	**5.01**	**<0.001****

Sd: Standard deviation, t: Independent t test, *: Significant, **: highly significant
LVEDD: Left ventricular end diastolic diameter, LVESD: Left ventricular end systolic diameter, IVS: Interventricular septum, PW: Posterior wall, EF: Ejection fraction, FS: Fractional shortening

This table shows that there was a statistical significance decrease in platelets count among cases group compared to control group.

Table (4): Laboratory results among the studied groups

Variable		Cases (n=40)	Control (n=40)	Test	P
Hb (gm/dl)	Mean ± Sd	10.77±2.12	10.92±1.66	0.36	0.71
WBC (x10^3/mm^3)	Mean ± Sd	9.19±2.28	10.46±2.26	0.94	0.35
Platelets (x10^3/mm^3)	Mean ± Sd	295.1±18.67	368.8±25.5	**2.54**	**0.01***
RDW (%)	Mean ± Sd	14.57±1.87	14.16±2.64	0.63	0.54
PDW (%)	Mean ± Sd	21.54±4.32	22.27±5.15	0.43	0.67

Sd: Standard deviation, Test: Independent t test and Mann Whitney test, *: Significant

This table shows that there was an increase in MR-proADM level among cases group compared to control group; the difference was highly statistically significant.

Table (5): MR-proADM level among the studied groups

Variable		Cases (n=40)	Control (n=40)	MW	P
MR-proADM (pg/ml)	Mean ± Sd	394.48±22.04	228.40±17.25		
	Median	346	190.32	**3.61**	**<0.001****

Sd: Standard deviation, MW: Mann Whitney test, **: highly significant (P<0.001)

This table shows that at cutoff 219.29 pg/ml, MR-proADM had sensitivity 70%, specificity 62.5% and accuracy 66.3% in diagnosis of heart failure.

Table (6): Validity of MR-proADM level in diagnosis of heart failure among the studied cases group

Cut off	AUC (95% CI)	Sensitivity	Specificity	PPV	NPV	Accuracy	P
219.29 pg/ml	0.73 (0.62-0.85)	70%	62.5%	65.1%	67.6%	66.3%	**<0.001 ****

AUC: Area under curve, CI: Confidence interval, PPV: +ve predicted value, NPV:,-ve predicted value, **: Highly significant

DISCUSSION

Our results showed that there were no statistical significant differences between the studied groups in mean age or sex distribution, as, study group (mean age was 2.39±1.56 and 70% males), and control group (mean age was 2.97±2.27 and 55% males). This came in agreement with **Zittermann *et al.*** [10] and **Narin *et al.*** [11] who found that there were no statistical significant differences between the studied groups in mean age or sex distribution.

This came in agreement with **Salem *et al.*** [12] who aimed in their study to evaluate the use of on-admission plasma levels of MR-proADM in diagnosing the clinical severity and progression of heart failure (HF) in children with CHD. Also, to correlate the levels of these biomarkers with the HF outcome (survival versus in-hospital mortality). There were 60 patients diagnosed to have HF compared with 30 healthy controls, age- and sex matched. No significant differences occur between HF group and healthy participants for the demographic data.

Also, **Hauser *et al.*** [13] aimed in their study to assess the diagnostic utility of novel biomarkers in pediatric HF. The results demonstrated that a total of 203 subjects were enrolled for the study (95 female; median age 7.5 years; IQR 2.4–13.0; range 5 days–24 years). This included 114 patients with HF (59 female; median age 5.9 years; IQR 2.1–12.5) and 89 controls (36 female; median age 8.9 years; IQR 2.7–14.5). No significant differences in sex or age distribution were found between the groups.

In the current study clinical findings among the studied cases group showed that most frequent symptoms among the studied cases were cough (95%), fever (95%), dyspnea (65%), cyanosis (65%) and difficult feeding (65%). Regarding Ross scoring class 47.5% were class IV, 22.5% were class I, 20% were class II and 10% were class III.

This came in agreement with **Sharmin *et al.*** [14] who found that of the different clinical features, cough, cyanosis, feeding problems, fast breathing, chest in drawing, poor weight gain, anemia, clubbing, were the major ones and this observation were correlated well with other studies in Bangladesh [15], India [16] and western countries [17]. **Roy *et al.*** [18] found that cough was present in 44.5%, fever in 44.5%, feeding problem in 36.4%, dyspnea on exertion in 29.1%, hyper cyanotic spell in 23.6% and convulsion in 4.8 (%) patients.

In the present study, there was a statistical significance increase in IVS and PW and statistical significant decrease in EF and FS among cases group compared to control group. As IVS (study group 6.58±1.75 and control group 6±0), PW (study group 6.41±1.74 and control group 5.57±0.94), EF (study group 59±15.21 and control group 74.22±5.63), and FS (study group 31.05±11.11 and control group 40.2±3.2), while there was no significant difference regarding LVEDD and LVESD.

This came in agreement with **Narin *et al.*** [11] who found that there was a statistically significant decrease in EF and FS in the patient group compared to the control group, while there was a significant increase in LVEDD in the patient group compared to the control group.

In the current study, there was a statistical significance decrease in platelets count among cases group compared to control group (study group 295.1±118.67 and control group 368.8±125.5) while there was no significant difference regarding other laboratory data (other than the biomarkers levels).

Salem *et al.* [12] found that no significant differences occur between HF group and healthy participants for the laboratory data (other than the biomarkers levels).

In the current study, there was a statistical significance increase in MR-proADM level among cases group compared to control group (study group 394.48±212.04 and control 228.40±107.25).

This came in agreement with **Salem *et al.*** [12] who found that the plasma levels were of MR-proADM (study group 184.373 ± 136.07 and control group 27.353 ± 16.4) on admission with significant difference between the studied groups. Also, **Hauser *et al.*** [13] found that there was a significant difference between groups for MR-proANP. **Pousset *et al.*** [19] **and Yu *et al.*** [20] found that plasma levels of ADM are elevated in HF and further correlate to disease severity.

The clinical application of ADM is limited because of its short half-life in plasma and instability [21]**.** For that reason, commercial immunoassays of more stable analyte, mid-regional fragment of proadrenomedullin (MRproADM) that could stoichiometrically be related to ADM, have been developed [22]**.**

In the current study, validity of MR-proADM level in diagnosis of heart failure among the studied cases group showed that at cutoff 219.29 MR-proADM had sensitivity 70%, specificity 62.5% and accuracy 66.3% in diagnosis of heart failure.

Also, **Khan *et al.*** [23] found that in patients with chronic HF, MR-proADM was identified as an

independent predictor of diagnosis. **Salem *et al.* [12]** said that MR-proADM at cutoff point (126.055) has sensitivity (60%), specificity (76%), positive predictive value (71.43%), and negative predictive value (65.25%), with area under the curve (AUC = 0.523), which was unacceptably low and not significant in prediction of accuracy of the test. **Hauser *et al.* [13]** found that ROC analysis showed poor accuracy for MR-proADM.

CONCLUSION

There is a high diagnostic value of measuring plasma level of MR-proADM at admission, regarding the diagnosis in the setting of pediatric congestive heart failure.

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