Diagnostic value of Serum Apelin Levels in Children with Heart Failure

Ahmed N.Gamil [1],Magdy MK Mahmoud, Moustafa Abd ElRheem, Mohammed Abdelrazek Abdelhakeem
Department of Pediatrics, Faculty of Medicine, Minia University, ElMinya, Egypt.
***Corresponding authors:**
Ahmed N.Gamil
Assistant lecturer, Pediatric Department, Faculty of Medicine, Minia University, El Minya, Egypt.
Email: masrawy1986rony@yahoo.com
Authors' affiliation
Magdy M.K Mahmoud
Professor of Pediatric Department, Faculty of Medicine, Minia University, El Minya, Egypt.
Email: magdymahmoud@gmail.com
Moustafa Abd ElRheem
Professor of Pediatric Department, Faculty of Medicine, Minia University, El Minya, Egypt.
Email: moustafaraheem@gmail.com
Mohammed Abdelrazek Abdelhakeem
Ass.Professor of clinical pathology Department, Faculty of Medicine, Minia University, El Minya, Egypt.
Email: mat_razek@hotmail.com

Short title: Aplein in heart failure

Abstract

neuroendocrine activation is typically found in patients with ،Apelin is an endogenous inotrope congestive heart failure (CHF). This activation includes, among others, the natriuretic peptides, which are secreted by the cardiac atria and ventricles as a response to volume and/or pressure overload. ANP has a vasodilator effect and may partly counteract the adverse effects of sympathetic activation in patients with HF.

Objective: We aimed to evaluate the prognostic value of aplein level in children with HF and its correlations with ANP.

Methods: Forty children with HF were included as a patient group. Twenty five healthy children matched for age, sex, and weight served as a control group. Chest X-ray, electrocardiogram (ECG), echocardiography, and laboratory investigations such as complete blood count, c-reactive protein, and serum apelin levels were performed for all included children at admission.

Results: Serum apelin level was significantly decreased in patients with HF at admission than healthy control group and this decrease went with advanced stage of HF. Serum ANP levels were significantly increased in patients with unfavorable prognosis than those with favorable prognosis.

Conclusion: Serum apelin level has a good predictive value for adverse outcome in children with HF.

Keywords Serum apelin ·ANP · Heart failure

***e*ISSN**1303-5150

DOI Number:10.14704/nq.2022.20.8.NQ44411 **NeuroQuantology 2022; 20(8): 3813-3817**

Introduction

Heart failure (HF) is a progressive clinical and pathophysiological syndrome which results when cardiac output is insufficient to meet the metabolic demands of various parts of the body [1]

Apelin's receptor is called APJ. The apelin/APJ system is a novel neurohormonal pathway that is widely represented in the heart and is an important regulator of cardiovascular homeostasis [4].

Apelin is a strong endogenous inotrope causes vasodilatation, decrease preload and after load, increases coronary blood flow and cardiac contractility [5].

Apelin has an antagonistic effect on the RAS system which plays an important role in the development and progression of HF [6].

RAS activation disables the apelin cardioprotective effect and down regulates APJ system [7]. Apelin level found to be increased at early stage of HF and progressively decreased in the advanced stages of the disease [8].

Atrial natriuretic peptide (ANP) or atrial natriuretic factor (ANF) is a natriuretic peptide hormone secreted from the cardiac atria that in humans is encoded by the NPPA gene.[1]

The main function of ANP is causing a reduction in expanded extracellular fluid (ECF) volume by increasing renal Sodium excretion. [4]

ANP is synthesized and secreted by cardiac muscle cells in the walls of the atria in the heart and these cells contain volume receptors which respond to increased stretching of the atrial wall due to increased atrial blood volume. [5]

Reduction of blood volume by ANP can result in secondary effects such as reduction of extracellular fluid (ECF) volume, improved cardiac ejection fraction with resultant improved organ perfusion, decreased blood pressure, and increased serum potassium. [6-8]

Patients and method

This study was carried out at the pediatric department, Minia University Hospital in the period from December 2020 to November 2021. It was conducted on 40 children presented with signs and symptoms of congestive heart failure (CHF) as a patient group. Twenty five healthy children of matched age and sex served as a control group. The study has been approved by the local ethical committee of our faculty of medicine. Informed consent was signed by all parents of included children.

Inclusion criteria: any child presented with signs and symptoms of CHF.

Exclusion criteria: age > 18 years, sepsis, multiple congenital anomalies, dysmorphology.

- Echocardiography using vivid 7 Ultrasound machine (GE medical system, Horten, Norway, with a 4S MHZ multi-frequency transducer). Left ventricular end systolic dimension (LVESD), left ventricular end diastolic dimension (LVEDD), and right ventricu- lar diameter (RVD) were measured. Left ventricular systolic function was evaluated as LV ejection frac- tion (EF%) where EF% = (LVEDD)3 − (LVESD)3/ (LVEDD)3 × 100% and LV fractional shortening (FS%) where FS% = (LVEDD) − (LVESD)/(LVEDD) × 100%. Left ventricular diastolic function was evaluated by E/A ratio where E wave represented passive LV filling and A wave represented atrial contraction.
- Serum apelin measurement: using enzyme-linked immunoassay assay (ELIZA) technique (Chongqing Biospes Co., Ltd).

Statistical analysis

Statistical analysis was performed using SPSS V.17 (SPSS Inc. Chicago, IL, USA). All continuous data were presented in the form of mean ± standard deviation (SD). Categorical data were presented in the form of number and percentage. Normal distribution of the data was checked by Shapiro–Wilk test. For comparing the mean of continuous variables between the two groups, we used independent *t* test. To compare non-parametric variables between the two groups, we used Chi-square test or Mann–Whitney U test. Difference between mean of serum apelin levels in various ROSS classification was performed using one-way analysis of variance (ANOVA) test. Post hoc

*e*ISSN1303-5150 www.neuroquantology.com

analysis was carried out using Bonferroni test. Receiver operating characteristics (ROC) curve was carried out to assess the prognostic value of serum apelin level for adverse outcome in in children with HF at different cutoff points. *P* value < 0.05 was considered significant.

Results

Demographic, clinical, and laboratory data were presented in Table 1. The study included 40 children diagnosed to have HF due to different causes (25males,15females) with mean age of (9.41±1.60) months and mean weight of (9.1 ± 1.6) kg. *Table 1*

Tewenty five healthy children served as a control group (15males, 10 females) with mean age of (9.04±1.35) months and mean weight of (13.3 ± 2.3) kg. No significant difference was present between the patient and control group as regards age and sex. *Table 1*

Weight was lower in children with HF than control (*P* < 0.001).

Serum apelin levels were significantly lower in patient group than control group (*P* < 0.001). *Table 2*

Serum ANP levels were significantly higher in patient group than control group (P < 0.001). *Table 2*

While LV FS, LV EF, and LV E/A ratio were significantly lower in patient group than control group (*P* < 0.001) reflecting impaired LV systolic and diastolic functions. *Table 3*

Discussion

In our study, serum apelin levels were found to be significantly decreased in children with HF than healthy control. This came in agreement with the results of Schrier RW, and Abraham WT.2019 demonstrated that patients with HF had elevated serum apelin levels in the early stage that decreased progressively as the disease worsened.[1]

Serum apelin levels were found to be inversely significantly correlated with Ross classification of HF denoting severity of HF. Interestingly, serum apelin level was significantly decreased in patients with bad prognosis than those with good prognosis.

Our results show Plasma levels of the atrial natriuretic peptide (ANP) are elevated in heart failure and significantly correlated with Ross classification of HF denoting severity of HF.]

Our study suggested that serum apelin level may have a prognostic role in children with HF. However, **Bjelland I.et al., 2020**. reported no prognostic role of apelin in HF patients and explained that serum apelin levels in their patients with acute HF were not different from that of control and they did not use apelin-13 which is the main form of apelin in cardiac tissue and human plasma.[12]

While, **Appels A.et al.,2017** study showed no prognostic value for apelin in patients with HF as they studied patients with chronic advanced HF who are candiated for cardiac transplantation in whom apelin–APJ system is completely overwhelmed and down regulated.[13]

Compliance with Ethical Standards

Conflict of interest All authors have no potential conflict of interest to disclose.

Ethical Approval The study is in accordance with the ethical standards of institutional research committee

Informed Consent Informed consents were obtained from all indi- vidual participants included in the study.

Authors' information

Available

Ethics approval and consent to participate

Written consents were obtained from patients' caregivers for patients less than 16 years old. The study was conducted According to the declarations of Helsinki and

Approved from the faculty of medicine scientific committee in Minia University (No: 116-5-2020).

Consent for publication

Not applicable

Competing interests

The authors declare that they have no competing interest

Funding

Personally funded by the authors.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' Contributions:

A,G and MR participated in the study design, data collection an interpretation and wrote the manuscript. AG and MRanalyzed the immunological data and AG participated to discuss the results and to write the manuscript.MA supervised the research group.All authors listed in a manuscript have contributed substantially to the work and seen revise and approved the submitted version.

Abberivations; AN P atrial natriuretic peptide ,CHD congenital heart disease, CTR cardiothoracic ratio, LV left ventricle, FS fraction shortening,
EF ejection fraction, EDD end-diastolic dimension, ESD end-systolic
dimension, RVD right ventricular diameter

REFERENCES

1. Schrier RW, Abraham WT. Hormones and hemodynamics in heart failure. N Engl J Med 2019;341:577–85.
2. Wei CM, Heublein DM, Perrella MA, Lerman A, Rodeheffer RJ, McGregor CG, Edwards WD, Schaff HV, Burnett JC Jr. Natriuretic peptide system in human heart failure. Circulation 2013;88:1004–9.
3. Persson H, Andreasson K, Kahan T, Eriksson SV, Tidgren B, Hjemdahl P, Hall C, Erhardt L. Neurohormonal activation in heart failure after acute myocardial infarction treated with beta-receptor antagonists. Eur J Heart Fail 2020;4:73–82.
4. Floras JS. Sympathoinhibitory effects of atrial natriuretic factor in normal humans. Circulation 2010;81:1860–73.
5. Persson H, Andreasson K, Kahan T, Eriksson SV, Tidgren B, Hjemdahl P, Hall C, Erhardt L. Neurohormonal activation in heart failure after acute myocardial infarction treated with beta-receptor antagonists. Eur J Heart Fail 2002;4:73–8. 6. Wiedemann K, Jahn H, Kellner M. Effects of natriuretic peptides upon hypothalamo-pituitary-adrenocortical system activity and anxiety behavior. Exp Clin Endocrinol Diabetes 2020;108:5–13.
7. Ströhle A, Jahn H, Montkowski A, Liebsch G, Boll E, Landgraf R,
Holsboer F, Wiedemann K. Central and peripheral administration of
atriopeptin is anxiolytic in rats. Neuroendocrinology 2017;65:210–5.
8. Wiedemann K, Jahn H, Yassouridis A, Kellner M. Anxiolytic-like effects of atrial natriuretic peptide on cholecystokinin tetrapeptide-induced panic attacks: preliminary findings. Arch Gen Psychiatry 2021;58:371–7.
9. Murberg TA, Bru E, Svebak S, Aarsland T, Dickstein K. The role of objective health indicators and neuroticism in perceived health and psychological well-being among patients with chronic heart failure. Pers Individ Dif 2017;22:867–75.
10. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand 2013;67:361–70.
11. Herrmann C. International experiences with the Hospital Anxiety and Depression Scale – a review of validation data and clinical results. J Psychosom Res 2017;42:17–41.
12. Bjelland I, Dahl AA, Haug TT, Neckelmann D. The validity of the
Hospital Anxiety and Depression Scale – an updated literature review.
J Psychosom Res 2020;52:69–77.
13. Appels A, Hoppener P, Mulder P. A questionnaire to assess premonitory symptoms of myocardial infarction. Int J Cardiol 2017;17:15–24.
14- Azevedo ER, Newton GE, Parker AB,
Floras J, Parker JD. Sympathetic response to atrial natriuretic peptide in patients with congestive heart failure. J Cardiovasc Pharmacol 2020;35:129–35.

Table 1:Demographic Data of Groups

Parameters	Patients (N = 40)	Control (N = 25)	P-value
Age (years)	4-12 9.41±1.60	7-11 9.04±1.35	0.25
Sex (M/F)	25M/15F	15M/10F	0.84
Weight (kg)	9.1 ± 1.6	13.3 ± 2.3	0.0001
Height (cm)	100-164 134.82±10.68	116-152 104.92±53.14	0.002

Table 2: Laboratory Data of Groups

Parameters	Patients (N = 40)	Control (N = 25)	P-value
Aplein (ng/L)	0.20-0.60 0.38±0.11	1.5-4.5 2.73± 0.76	0.0001
ANP (ng/mL)	4-11 7.42±1.62	0.90-2.5 1.86±0.43	0.0001

Table 3: ECHO Findings of Groups

Variable	Patient (*N* = 40)	Control group*P* (*N* = 25)	P-value
CTR	61 ± 7	50 ± 1	< 0.001*
LV FS%	22 ± 1	34 ± 2	< 0.001*
LV EF%	42 ± 1	64 ± 1	< 0.001*
LV E/A ratio	0.8 ± 0.1	1.3 ± 0.2	< 0.001*
LVEDD (cm)	2.6 ± 0.7	2.2 ± 0.3	0.003*
LVESD (cm)	1.7 ± 0.5	1.3 ± 0.4	0.006*
RVD (cm)	1.3 ± 0.4	1.1 ± 0.2	0.04*