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ORIGINAL ARTICLE

B Type Natriuretic Peptide (BNP) As Diagnostic and Prognostic Biomarker in Children with Congestive Heart Failure

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ABSTRACT

Background: Pediatric acute heart failure is now being increasingly recognized as an important source of healthcare resource utilization. B-type natriuretic peptide (BNP) continues to be the dominant biomarker in pediatric heart failure. This study aimed to prove the role of BNP in diagnosis and prognosis of congestive heart failure in children.

Method: This case-control study was performed in Zagazig University Hospitals and include 60 infants and children who were divided into 2 groups: group 1 consisted of 30 children diagnosed by congestive heart failure, and group 2 consisted of 30 age and sex-matched apparently healthy children. Serum BNP levels were measured for both groups with assessment of the cardiac function, CBC, CRP and serum creatine level.

Results: BNP is significantly higher among CHF patients compared to controls. BNP is found to be higher in patients with severe heart failure compared to moderate and mild HF patients with significant correlation. BNP is found to be higher among congestive heart disease patients with sensitivity of 93.3% and specificity of 76%. BNP is a significant independent diagnostic parameter for CHF. BNP is found to be non-significant prognostic factor for children with CHF.

Conclusions: BNP continues to be the dominant biomarker in pediatric heart failure. BNP is a significant diagnostic marker in diagnosis of heart failure, while it found to be non-significant prognostic factor in CHF.

Key words: BNP; Congestive; Heart; Failure; Congenital.

INTRODUCTION

Pediatric acute heart failure is now being increasingly recognized as an important source of healthcare resource utilization. The underlying mechanisms and etiology responsible for pediatric heart failure are very heterogeneous from simple congenital heart defects, and cardiomyopathies to complex palliated single ventricle patients. Similar to the underlying etiologies, management and outcomes in these groups of patients are also very variable. However, the ability to prognosticate outcomes in pediatric heart acute heart failure is extremely limited due to lack of data [1]. Current American Heart Association guidelines for the management of heart failure emphasize the role of cardiac biomarkers in the diagnosis, management, and prognostication of heart failure [2].

Of all the biomarkers reviewed, B-type natriuretic peptide (BNP) continues to be the dominant biomarker even in pediatric heart failure. BNP belongs to a larger family of titrated peptides that have a paracrine role in the body. It is primarily secreted by cardiomyocytes in the form of pre-pro-peptides. These pro-peptides are synthesized within the endoplasmic reticulum of the cardiac cells where they're stored as specific atrial granules. These pre-pro-peptides have a constant basal rate of release and play an important regulatory function in the maintenance of salt and water homeostasis. Various stimuli such as myocardial stretch or stress can lead to a very rapid increase in the secretion of these pre-pro-peptides. Once released it undergoes conversion into pro BNP which is cleaved by serine peptidases into the

active moiety BNP and inactive moiety NT-proBNP [3]. This study aimed to study the serum level of BNP as a diagnostic and prognostic cardiac biomarker in congestive heart failure.

METHODS

This study was performed in the pediatric cardiology unit, pediatrics department, Zagazig University Hospitals from January 2019 to December 2019. This case-control study included 30 patients diagnosed as CHF (15 males and 15 females), their ages ranged from (2-48) months and 30 clinically healthy control children with matched ages and sex (18 males and 12 females), their age ranged from (3-53) months. Control children were selected after careful clinical examination, they were completely free from any disease.

Inclusion criteria: Include children with congestive heart failure due to congenital heart disease or dilated cardiomyopathy, both male and female included with ages ranging from 2m to 48m.

Exclusion criteria: Include heart failure due to causes other than congenital heart disease or cardiomyopathy, infants with previous surgical cardiac correction, kidney or liver diseases, inflammatory and autoimmune disorders, infections, and malignancies.

Methods: Patients and controls underwent full history taking and clinical examination including general, chest, cardiac and abdominal examination. Patients were classified according to modified Ross grading regarding the severity of HF [4], Follow up as done for all cases for 6 months to detect survivors and non-survivors.

Transthoracic echocardiography (TTE) using esaotie MyLab™Class C systems, echocardiographic measurements including M mode left ventricular end-diastolic diameter (LVEDD) and end-systolic diameter (LVESD), Septal (IVS) and posterior wall (PW) thickness, EF% and FS% were measured according to **Sneider et al** [5]. Ejection Fraction (EF%) was calculated from the formula

$$EF = \frac{LVEDD - LVESD}{LVEDD} \times 100$$

Fractional shortening (FS%) was calculated from the formula: FS = (LVEDD-LVESD/LVEDD) x 100.

A blood sample was obtained from each child and a complete blood picture (CBC) was measured by an automated blood counter on Sysmex® XS 500 Japan also serum creatinine by colorimetric assay on INTEGRA 400 Roche. C-reactive protein (CRP) using Immunoturbidimetric assay for quantitative determination of CRP in human serum on Roche Cobas C 501 analyzer. Serum BNP level by Human B-type natriuretic peptide (BNP) ELISA Kit by SunRed Co., LTD. Catalogue No. 201-12-2183.

Written Informed consent was taken from the patient parents and/or their caregivers. The permission for the study was received from the Pediatrics Departments of Zagazig University Hospitals after the permission of the Institutional Review Board (IRB). The research was carried out in compliance with the Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

STATISTICAL ANALYSIS

Data were tested for normal distribution using the Shapiro Walk test. Qualitative data were represented as frequencies and relative percentages. Chi-square test ($\chi 2$) and Fisher exact were used to calculate the difference between qualitative variables as indicated. Quantitative data were expressed as mean ± SD (Standard deviation) for parametric and median and range for non-parametric data. Independent T-test and Mann-Whitney test were used to calculate the difference between quantitative variables in two groups for parametric and non-parametric variables respectively.Kruskal Wallis test was used to compare more than two dependent groups of non-parametric variables respectively. Regression analysis using the stepwise method was used to determine the potential diagnostic and prognostic detectors of CHD. Receiver operating characteristic (ROC) curve was constructed to permit the selection of threshold values for test results and the comparison of different testing strategies. Areas under ROC curves and their standard errors were determined using the method of Cantor and compared using the normal distribution, with correction for correlation of observations derived from the same cases.

All statistical comparisons were two-tailed with a significance level of P-value $\leqslant$ 0.05 indicating significance, and p 0.05 indicates a non-significant difference.

RESULTS

In our study, the ages of CHF patients ranged from 2m to 48m with a median of 7.5m, 50% of cases were females and 50% were males, age and sex were matched with controls as their ages ranged from 3m to 53m with a median of 7m, 40% of controls were females and 60% were males. Cases and controls were comparable in height as cases' height ranged from 58.1 – 95.1 with a mean of 71.88 ± 10.18 and controls height ranged from 58.4–102.5 with a mean of 70.03 ± 11.28, but CHF patients had a significant lower weight as their weight ranged from 3 – 8.6 with mean 5.66 ± 1.49, 76.7% of them (23 patients) suffering from failure to gain weight compared to the controls which their weight ranged from 4.7 – 14 with mean 7.59 ±

2.82. Congenital heart diseases represented 77% of cases while dilated cardiomyopathy represented 23%. We found that the case group had significantly higher values regarding heart rate, respiratory rate, temperature, and blood pressure compared to controls. We also found that serum creatinine was significantly lower among CHF cases compared to controls. (Table 1). The case group showed a highly significant increase in left ventricular end-systolic diameter (LVESD), left ventricular end-diastolic diameter (LVEDD), and PAP in patients with CHF compared to controls, meanwhile, EF and ES values showed a significant decrease in patients compared to controls. The *E/A ratio showed a non-significant difference. (Table 2). According to modified ross score, CHD patients had a significantly more frequent percentage of moderate heart failure (43.3%)5 and severe HF (26.1%), while all cardiomyopathy patients had severe HF.In our study, we observed that BNP was significantly higher among CHF patients compared to controls. BNP was also found to be higher in patients with severe heart failure compared to moderate and mild HF patients without statistical significance difference (Table 3) but with significant correlation (Table 4). A non-significant difference was found between pulmonary hypertension patients and non-pulmonary hypertension patients regarding BNP with a median of 51.11 in the pulmonary hypertension group and 69.92 in the non-pulmonary hypertension group. There was also no correlation found between BNP and CHD with a median of 54.05, dilated cardiomyopathy with a median of 53.95, or between BNP and other parameters except with modified Ross grading (Table 4). Using multivariant regression analysis, BNP is proved to be a significant independent diagnostic parameter for CHF. BNP was also found to be a non-significant prognostic factor in children with CHF (Table 5). Roc curve detected area under curve (AUC) 0.923 (Fig 1). BNP at cutoff point >76.9 showed a sensitivity of 93.3% and specificity of 76%, PPV of 91.7%, and NPV of 84.6% with an accuracy of 89%. There was a significant difference between the survivor and non-survivor patients in the modified Ross, but no significant difference was found in the rest parameters. BNP showed a higher level in non-survivor patients but without a statistical significant difference (Table 6).

Table 1: Vital and laboratory parameters of the studied groups.

	Cases (n=30)	**Controls (n=30)**	**T**	**P**
HR (b/min) Mean ± SD	171.7 ± 10.88	120.8 ± 11.35	**17.734**	**0.000**
RR (b/min) Mean ± SD	69.13 ± 7.37	29.17 ± 3.62	**26.698**	**0.000**
Temperature (°C) Mean ± SD	37.78 ± .43	37.12 ± .68	**5.646**	**0.001**
SBP (mmHg) Mean ± SD	105.27 ± 10.64	94.31 ± 6.78	**8.722**	**0.001**
DBP (mmHg) Mean ± SD	73.42 ± 11.35	66.05 ± 4.72	**7.411**	**0.001**
Hemoglobin (g/dl) Mean ± SD	11.42 ± 1.99	11.54 ± 1.535	0.330	**0.823**
TLC (10^3 /µL) Mean ± SD	9.61 ± 1.952	10.81 ± 1.26	1.471	**0.112**
PLT (10^3 /µL) Mean ± SD	257.2 ± 35.48	260.47 ± 34.88	1.234	**0.242**
Creatinine (mg/dl) Median (Range)	0.1 (0.1 – 0.6)	0.3 (0.2 – 0.6)	**MW 4.105**	**0.001**
CRP (mg/dl) Median (Range)	**2.25 (0.3 – 11.3)**	**2.75 (0.6 – 5.3)**	**MW 0.796**	**0.429**

DBP:diastolic blood pressure HR: heart rate
RR: respiratory rate
SBP: systolic blood pressure
CRP: C-reactive protein. MW: Mann Whitney
PLT: Platelets count
TLC: total leucocytes count

Table 2: Echo features among the studied group

Variables	Cases (n=30)	Controls (n=30)	T	P
LVEDD Mean ± SD	32.37 ± 12.87	20.47 ± 1.79	**5.015**	**0.000**
LVESD Mean ± SD	22.5 ± 11.05	14.6 ± 1.59	**3.875**	**0.000**
E/A ratio Mean ± SD	1.33 ± 0.531	1.27 ± 0.341	1.361	**0.152**
EF (%) Mean ± SD	45.97 ± 11.63	65.13 ± 3.88	**8.561**	**0.000**
FS (%) Mean ± SD	18.5 ± 3.05	35.74 ± 4.15	**8.041**	**0.000**
PAP (mmHg) Mean ± SD	**40.3 ± 17.96**	**20.82 ± 4.88**	**5.548**	**0.000**

EF: Ejection fraction.
FS: fractional shortening
LVEDD: left ventricular end-diastolic diameter. LVESD: left ventricular end-systolic diameter PAP: pulmonary artery pressure

Table 3: Serum BNP level between the two studied groups and its relation to severity of heart failure.

	Cases (n=30)			Controls (n=30)	MW/*KW*	P
BNP (ng/l) Median (Range)	54.01 (5.12 – 90.45)			5.19 (0.2 – 7.44)	***mw*** **8.566**	**0.000**
	Mild (n=4)	**Moderate** (n=13)	**Severe** (n=13)			
	10.64 5.12 – 86.33	**54.05 10.53 – 89.29**	**68.59 11.85 – 90.45**		***kw*** **1.730**	**0.196**

MW: Mann Whitney
KW: Kruskal Wallis

Table 4: Correlation of BNP with different parameters among cases group.

Parameters	BNP	
	R	**p**
Age	0.108	**0.570**
Weight	0.024	**0.900**
Height	-0.022	**0.909**
HR	-0.128	**0.501**
RR	-0.079	**0.677**
SBP	0.293	**0.086**
DBP	0.346	**0.122**
Hb	-0.148	**0.435**
Creatinine	0.324	**0.080**
CRP	-0.143	**0.451**
LVEF%	-0.314	**0.091**
LVEDD	0.025	**0.895**
LVESD	0.102	**0.591**
E/A	-0.023	**0.906**
PAP	-0.132	**0.488**
LVFS%	-0.226	**0.230**
Modified Ross grading	**0.529**	**0.016***

HR: heart rate DSP: diastolic blood pressure
LVEF: left ventricular ejection fraction SBP: systolic blood pressure
RR: respiratory rate LVFS: left ventricular fractional shortening LVEDD: left

ventricular end-diastolic diameter. PAP: pulmonary artery pressure
LVESD: left ventricular end-systolic diameter CRP: C reactive protein
Hb: hemoglobin

Table 5: Multivariate regression analysis to identify the potential diagnostic and prognostic value of BNP for congestive heart failure**.**

					95% Confidence Interval for B	
	B	**S.E.**	**B**	**Sig.**	Lower Bound	**Upper Bound**
BNP (Diagnostic marker)	0.441	0.002	0.911	**.000***	0.010	**1.018**
BNP (Prognostic marker)	**-0.002**	**0.004**	**-0.102**	**0.704**	**-0.010**	**0.007**

BNP: brain type natriuretic peptide

Table 6: Relations of different parameters in the cases group according to their outcome.

		Survived (n=21)	**Non-survived (n=9)**	**Test**	**P**
Age (months) Median Range		7 2 – 48	8 4 – 36	MW 1.517	**0.141**
EF (%) Mean ± SD		47.24 ± 11.64	43 ± 11.73	t 0.912	**0.370**
FS (%) Mean ± SD		18.67 ± 3.28	18.11 ± 2.57	t 0.451	**0.655**
Creatinine (mg/dl) Median Range		0.1 0.1 – 0.6	0.1 0.1 – 0.3	MW 0.586	**0.563**
BNP (ng/l) Median Range		53.95 5.12 – 90.11	80.76 11.85 – 90.45	MW 0.516	**0.610**
Modified Ross	**Mild**	4 (19%)	--	χ^2 **16.813**	**0.000**
	Moderate	12 (57.1%)	1 (11.1%)		
	Severe	**5 (23.8%)**	**8 (88.9%)**		

EF: left ventricular ejection fraction
FS: fractionl shortening
BNP: brain type natriuretic peptide

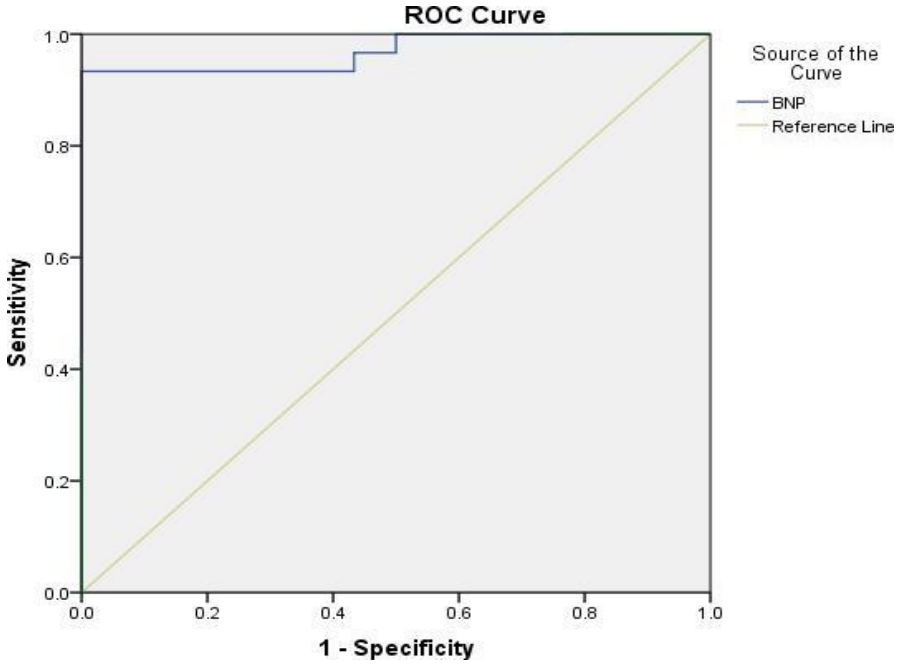

Figure 1. ROC of BNP as diagnostic markers for congestive heart failure in children.

DISCUSSION

Failure to thrive in CHD appears to be multi-factorial and may differ in etiology from patient to patient. It includes the underlying cardiac anomaly, hemodynamic factors, hypoxemia, inadequate caloric intake, or macronutrient intake, increased energy consumption relative to intake, increased inflammation, or associated comorbidities that include gut dysfunction, respiratory infections, associated genetic syndromes, and reduced birth weight [6]. Our CHF patients had a significantly lower weight compared to the controls, with 76.7% of them (23 patients) suffering from failure to gain weight. Parallel to our findings, **Hasija et al**. [7] and **Zoair et al**. [8] reported a similar finding. However, cases and controls were comparable in height without statistically significant differences as they were almost from the same age group and most of the cases were under the age of one year. So, the illness is too early to affect the height.

Regarding symptoms, the most prevalent symptom was tachycardia by 90%, we found that CHD patients have significantly higher heart rates compared to controls. Dutra et al. [9] reported similar findings. This may be due to myocardial hypertrophy and stretch with increased preload and afterload. Myocardial fibrosis and scar-altered calcium handling in the failing heart also can cause ventricular tachycardia [10]. our CHF patients had significantly higher respiratory rates compared to controls. Marr.[11] reported similar findings. Patients with HF often show a restrictive respiratory pattern secondary to heart enlargement, increase lung fluids, and impairment of alveolar capillary gas diffusion, this leads to an increased respiratory rate [12].

The CHF group had significantly higher systolic and diastolic blood pressure values compared to controls. **Dutra et al.** [9] demonstrated that the increase in SBP and DBP in CHD is more related to fear and anxiety. However, an inverse correlation has been established between blood pressure and vasopressin. CHF patients are known to have decreasing blood pressure with increasing severity of the disease [13]. Temperature of case group had significant higher values compared to controls. Similarly, **Benda et al.** [14] documented similar finding. On the other hand, **Balmain et al**. [15] found lower temperature in HF when compared to controls.

Regarding CBC parameters, hemoglobin, TLC, and platelet count were statistically non-significant in both groups. **Goldberg et al.** [16]. found that anemia occurs commonly in children hospitalized for acute heart. **Polat et al.** [17] observed that decreased platelet and lymphocyte counts were independently correlated with one-year mortality in 119 hospitalized subjects with heart failure and reduced EF. CRP values in cases show a non-significant difference compared to controls. **Anand et al**. [18] found that CRP levels increase in heart failure patients and higher levels are associated with features of more severe heart failure. Moreover, we found that median creatinine levels were significantly lower in heart failure children compared to controls. **Hari et al.** [19] perform a study on 154 boys, 77 were malnourished and 77 were normally nourished, serum creatinine levels in malnourished boys were significantly lower than those in normally nourished boys. That could explain why cardiac children with a low weight according to age and without kidney injury had low serum creatinine levels compared to controls.

Regarding echocardiographic characteristics, we found a significant increase in LVEDD and LVESD in patients compared to controls. Meanwhile, EF, ES values showed a significant decrease in patients compared to controls. However, we found that E/A ratio show no statistical significance difference between the groups. **Mohamed.** [20] and **Zoair et al.** [8] reported similar findings.

The neurohormonal theory explains the major mechanism of heart failure. According to this theory, the level of BNP in the blood increases through the activation of the natriuretic peptide system. BNP was significantly higher in CHF patients compared to controls. **Sahin et al**. [21] reported similar results. **Law et al.** [22] found that BNP is a reliable test to diagnose significant structural or functional cardiovascular disease in children. According to modified Ross classification, the present study showed a significant difference between CHD and cardiomyopathy patients. That all cardiomyopathy

patients were severe Ross while the majority of CHD patients were moderate Ross 43.3%, followed by severe Ross 26.1% and mild Ross cases representing 13.3%. **Rossano et al**. [23] observed that children suffering from heart failure due to cardiomyopathy were associated with more severe symptoms, hospital stay, and mortality rate than children with HF due to congenital heart diseases. We found BNP level was higher in severe modified Ross HF patients compared to moderate modified Ross HF patients compared to mild modified Ross HF patients with a significant positive correlation. **Ross.** [24] reported that the N terminal fragment of the prohormone BNP and NT-proBNP is a good marker of clinical severity and worsening systolic function in children with HF. **Xu et al**. [25] and **Troughton et al.** [26] reported that serum BNP increased, and the degree of elevation correlated positively with the severity of HF. We also found that there was no significant relationship between BNP level and HR, SBP, and DBP. **Xu et al**. [25] reported the same results.

We found no association between LVEF, FS, and E/A ratio and BNP levels but negative correlations were found by **Hauser et al.** [27] between BNP level and FS, EF levels. BNP showed a non-significant correlation with age and RR. **Kes et al**. [28] found that there was no correlation with respiratory rate. However, Tao **He et al**. [29] found a correlation with age that can be explained in this study by a wide range of patient ages as it was performed in adult patients with ages from 60-80 years. We found that BNP is a significant independent diagnostic marker for CHF which was confirmed by multi-regression analysis at a cutoff of 76.9 ng/l was a significant diagnostic marker for CHF with a sensitivity of 93.3% and specificity of 61.90%. However, BNP was found to be a non-significant prognostic factor in children with CHF. Similarly, **Elsharawy et al**. [30] found that plasma levels of NT-proBNP with a cutoff value of101 fmol/ml (854 pg/ml), predicted CHF with a sensitivity of 90.0% and specificity of 80%.

When comparing the survivors and non-survivor patients, we only found a significant difference found in the modified Ross score as non-survival cases with severe modified Ross scores had a higher percentage (88.9%). **Neuhold et al**. [31] found a significant difference between the survivors and non-survivor patients regarding NYHA classification. We found that the survivors have lower BNP values but without statistically significant differences. This may be explained by our relatively small sample size. Parallel to our result, **Neuhold et al**. [31] found that BNP was significantly lower in survivors.

CONCLUSION

BNP level elevated in children with congestive heart failure and considered a significant diagnostic marker in CHF with a strong significant correlation with the severity of HF. BNP found to be non-significant prognostic marker in children with CHF.

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