Paediatrica Indonesiana

p-ISSN 0030-9311; e-ISSN 2338-476X; Vol.60, No.5(2020). p.277-82; DOI: 10.14238/pi60.5.2020.277-82

Original Article

Brain natriuretic peptide and atrial septal defect size in children

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Abstract

Background Atrial septal defect (ASD) is one of the most common forms of congenital heart disease (CHD). Brain natriuretic peptide (BNP) is a heart marker released into the circulation during pressure overload, heart volume expansion, and increased stress on +the myocardial wall.

Objective To assess for a possible association between atrial septal defect size and BNP level in pediatric patients.

Methods This cross sectional study on children with ASD was done from March to December 2018 in pediatric outpatients and inpatients at Dr. Wahidin Sudirohusodo Hospital, Makassar, South Sulawesi. Measurement of ASD defect was conducted using echocardiography and categorized as small defect (<3 mm), medium defect (3-8 mm), and large defect (>8 mm). Brain natriuretic peptide was measured using radioimmunoassay and immunoradiometricassay. Nutritional status was categorized using WHO if the patients aged younger than 5 years and NCHS for patients aged equal or more than 5-year-old.

Results Mean BNP levels were 65.5 pg/mL in the small ASD group, 273.2 pg/mL in the moderate ASD group, and in 654.5 pg/mL in the large ASD group, with significant differences among ASD groups. We found a significant positive correlation between BNP levels and ASD diameter (r=0.829; P=0.001), with Y regression equation of: (BNP level) =2.624 + 0.009X (ASD diameter in mm).

Conclusion Brain natriuretic peptide levels have significant positive correlation with ASD size. Hence, BNP measurements can be used to predict septal defect size in children with ASD. Acyanotic CHD patients with suspected ASD and high BNP levels may have moderate-to-large ASDs. **[Paediatr Indones. 2020;60:277-82; DOI: 10.14238/pi60.5.2020.277-82].**

Keywords: *atrial septal defect size; brain natriuretic peptide*

Congenital heart disease (CHD) is the most common heart disorder affecting infants and children. It is found in 8 of every 1,000 live births, with one-third manifesting as a critical condition in the first year of life, and causing death in 50% of emergencies in the first month of life.[1] A Taiwanese study showed a slightly higher prevalence of 13.08 of 1,000 live births, in which around 12.05 occurred in male babies. The most common CHD is ventricular septal defect.[2] Congenital heart disease is divided into two types, cyanotic and acyanotic. Cyanotic CHD is characterized by central cyanosis due to right-to-left shunts, including tetralogy of Fallot (TF), transposition of the great arteries (TGA), and double-outlet right ventricle (DORV). Acyanotic CHD can be divided into three groups based on hemodynamics: (1) left-to-right shunts such as persistent ductus arteriosus (PDA), atrial septal defect (ASD), and ventricular septal defect (VSD); (2) right

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Submitted March 17, 2020. Accepted September 17, 2020.

heart obstruction such as pulmonary valve stenosis; and (3) left heart obstruction such as aortic valve stenosis, coarctation of the aorta, and mitral stenosis.[3]

Atrial septal defect is the second most common CHD, with an incidence of around 18% of all CHDs. Hemodynamic disorders that occur in ASD are caused by left-to-right shunts due to a defect in the atrial wall of the heart. As a result, blood from the left atrium, which is supposed to enter the left ventricle, enters the right atrium then the right ventricle. If the hole is large enough, it can increase the load volume of the right heart, while also increasing the load volume of the left heart. There are three types of ASD: secundum ASD (50-70%), primum ASD (30%), and sinus venous type ASD (10%).[3]

B-type natriuretic peptide (BNP) is a cardiac neurohormone originating from the granular membrane of the heart ventricles, which contributes to increased ventricular volume and high pressure. The BNP was initially found in pig brain and named brain natriuretic peptide (BNP). While this substance is also found in human brain, it is more commonly found in the heart, secreted by ventricular cardiomyocytes in response to increased tension of the heart muscle wall and pressure on ventricular filling. Therefore, BNP levels may have a correlation with defect size in ASD. The BNP examination has been suggested as a method for early detection of ASD complication. Echocardiography is typically used to diagnose CHD, but it is not readily available and is operator-dependent. Therefore, in order to detect and manage ASD complications in a timely manner, we aimed to assess for a relationship between BNP levels and heart defect size, with the hope of using BNP as a marker for ASD. With early treatment, children's morbidity and mortality can potentially be reduced.[4] We aimed to assess for a possible association between atrial septal defect size and BNP level in pediatric patients.

Methods

This cross-sectional study was conducted at Dr. Wahidin Sudirohusodo Hospital, Makassar, South Sulawesi, from March to December 2018. The independent variables were acyanotic CHD with large ASD < 3 mm, medium ASD 3-8 mm, and small ASD > 8 mm. The BNP examination was conducted at *Hasanuddin University Medical Research Centre* (HUMRC) using immunoradiometricassay (IRMA) method. Venous blood sample was collected without fasting before and 5-10 mL blood was stored into the tube without anticoagulation. The blood then was centrifuged with 3000 rpm speed for 10 minute, afterward the serum stored in the freezer (-200C).

Nutritional status for subjects aged > 5-years-old was classified using *NCHS*: well-nourished (actual weight/ideal height according to age 90-110%, undernourished (actual weight/ideal height according to age 70-< 90%, malnourished (actual weight/ideal height according to age < 70%). While for subjects aged ≤ 5-years-old was classified using *WHO*: well-nourished (weight for height -2 SD to +2 SD according Z score; undernourished weight for height -2 SD to -3 SD according Z score; malnourished (weight for height < 3 SD according Z score).

The subjects were recruited from pediatric outpatients and inpatients with ASD at Dr. Wahidin Sudirohusodo Hospital, Makassar, South Sulawesi, who met the inclusion criteria. Inclusion criteria were children with ASD 1 month-18 years of age whose agreed to join this study. Exclusion criteria were ASD with renal disease, sepsis, cancer, pulmonal stenosis, total anomalous pulmonary venous drainage (TAPVD). Subjects' data on age, sex, nutritional status, echocardiography, and BNP levels were collected from medical records. Echocardiographic results were interpreted by pediatric cardiologists, then validation and reliability were tested in the interpretation of electrocardiogram results.

Data were grouped based on size of defect small, moderate and large. The appropriate statistical methods were then chosen: univariate (mean, median, frequency and standard deviation) and multivariate analysis (one way anova test, Pearson correlation test). This study was approved by the Ethics Committee of the Universitas Hasanuddin Medical School.

Results

During the study period, there were 103 subjects consisted of 58 females (56.3%) and 45 males (43.7%). The mean age of subjects was 3 years 6 months, ranging from 6 months to 13 years 3 months. Subjects'

nutritional status was classified as malnourished (50; 48.5%), undernourished (27; 26.2%), or well-nourished (26; 25.2%) (**Table 1**).

Table 1. Subjects' characteristics

Characteristics	(N= 103)
Age, months	
Mean (SD)	43.74 (37.67)
Median (range)	28.00 (6-159.00)
Gender, n (%)	
Female	58 (56.3)
Male	45 (43.7)
Nutritional status, n (%)	
Well-nourished	26 (25.2)
Undernourished	27 (26.2)
Malnourished	50 (48.5)
ASD defect size, n (%)	
Small	33 (32)
Medium	35 (34)
Large	35 (34)
ASD diameter, cm	
Mean (SD)	5.5 (3.02)
Median (range)	5.7 (1.2-12.70)
BNP level, pg/mL	
Mean (SD)	336.24 (294.33)
Median (range)	214 (50-979.00)

Statistical analysis showed that there were significant differences between the mean BNP levels in the malnutrition group for malnutrition and good nutrition (**Table 2**).Bonferroni's post-hoc analysis revealed significant differences between mean BNP level differences in the undernourished *vs.* malnourished groups (397.756 pg/mL; P<0.000) and the malnourished *vs.* well-nourished groups (471.229 pg/mL; P<0.000). The mean BNP level difference between the undernourished *vs.* well-nourished groups was 73.472 pg/mL (P<0.00) (**Table 3**).

Table 2. BNP level based on nutritional status

BNP level, pg/mL	Nutritional Status		
	Malnourished (n = 50)	Under-nourished (n = 27)	Well-nourished (n = 26)
Mean	559.5	161.7	88.2
Median	609.0	100	63.0
SD	252.11	151.8	91.6
Range	67-979	50-577	50-454

One-way Anova test=62.607; P=0.001

Statistical analyses revealed significant differences in mean BNP level differences among the small, medium, and large ASD groups [small *vs.* medium (207.654 pg/mL; P<0.00), small *vs.* large (588,968 pg/mL; P<0.00), and moderate *vs.* large (381.314 pg/mL; P<0.00)] (**Table 4**).

Multivariate regression analysis was done on the two variables with significant correlations to BNP levels by univariate analyses. We found that ASD size and BNP level had a significant association (P=0.001), but nutritional status and BNP level did not (P=0.086) (**Table 5**).

Y regression equation of BNP level was 2.624 + 0.009X (ASD diameter in mm). Correlation analysis between BNP levels and ASD diameter showed that the correlation between BNP levels and ASD diameter was significant with P=0.000 (P<0.05) and r=0.829 with the Y regression equation (BNP level) =2.624 + 0.009X (ASD diameter in mm) (**Figure 1**). This finding indicates that using BNP level to estimate ASD size is equivalent to echocardiographic ability, with a regression equation of a 1 mm increase in ASD diameter for a 0.0009 pg/mL BNP increase. Spearman's correlation analysis of BNP level and ASD diameter revealed a significant correlation (P=0.0001and r=0.829) (**Figure 1**).

Discussion

Atrial septal defect is a common type of congenital heart disease (CHD) in children, with a prevalence of approximately 10-15% of CHD patients. Atrial septal defects can occur alone or in combination with other cardiac defects. Most children with ASDs do not show any clinical symptoms during childhood. However, some common clinical signs in pediatric patients with ASD are systolic ejection murmur and wide-fixed split. Similar heart sounds are often heard in children without ASD or other CHD types, which makes diagnosing ASD a challenge for clinicians. Thus, echocardiography is crucial in determining a diagnosis, in addition to history-taking and physical examination.[5]

In our study, ASD was more common in girls than boys (56.3% *vs.* 43.7%, respectively). A study in Taiwan also reported more CHD (ASD) in boys than girls, and there was no significant relationship

Table 3. Comparison of mean BNP level differences by nutritional status

Nutritional status	Difference in mean BNP level, pg/mL	95% CI	P value
Malnourished *vs.* undernourished	397.76	282.57 to 512.95	0.00
Malnourished *vs.* well-nourished	471.23	354.61 to 587.85	0.00
Undernourished *vs.* well-nourished	73.47	-59.05 to 206.56	0.54

Table 4. Comparison of mean BNP level differences and ASD size

ASD size	Difference in mean BNP level, pg/mL	95% CI	P value
Small *vs.* medium	207.654	109.961 to 305.347	0.000
Small *vs.* large	588.968	491.275 to 686.661	0.000
Medium *vs.* large	381.314	285.068 to 477.560	0.000

Table 5. Multivariate logistic regression analysis on BNP level with nutritional status and ASD size

Variables	B	SE	P value	95% CI
Nutritional status	-56.380	32.552	0.086	-120.961 to 166.595
ASD diameter	250.112	33.132	0.001	184.378 to 315.846
Constant	-69.215	118.858	0.562	-305.026 to 166.595

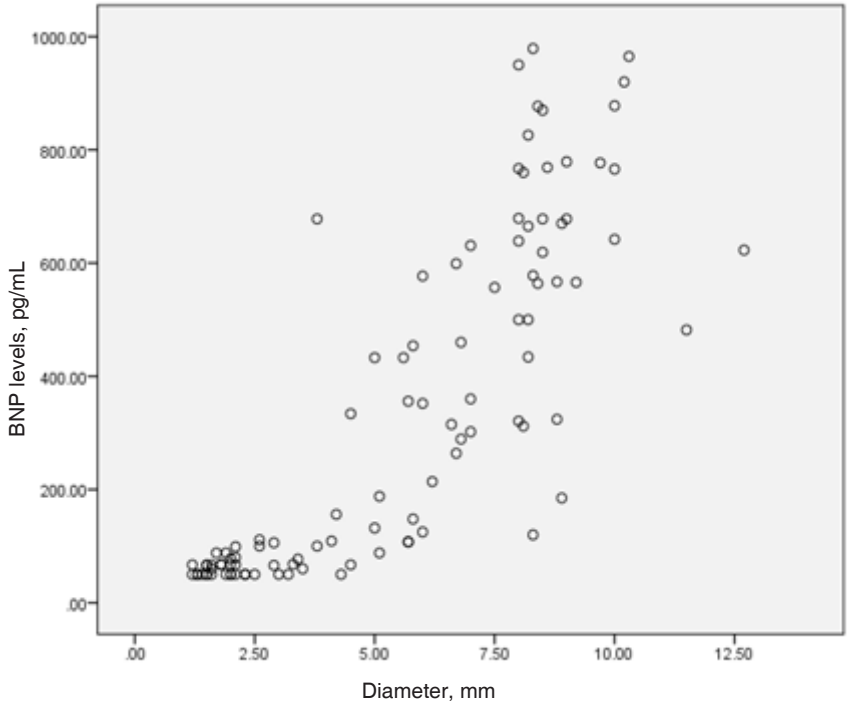

Figure 1. Correlation of BNP levels and ASD diameter

between sex and the size of the defect (P=0.605).[2] Our subjects' mean age was 3 years 6 months, with a median of 1 year 4 months. Mean ages of children according to defect size were 31.12 months for small, 32.4 months for moderate, and 67 months for large. One-way ANOVA test showed significant differences in age and ASD Size between small, medium, and large ASD (P=0.001).

In our study, nutritional status was classified as well-nourished (25.2%), undernourished (26.2%), and malnourished (48.5%). Similarly, a study in Jakarta showed a malnutrition prevalence in children with CHD of 51.1%, with 22.3% of them are malnourished.[6] In our study, there was a significant relationship between the size of the defect and the nutritional status of the patients (P=0.001). Poor nutritional status was more common in large ASD patients, while good nutritional status was more common in small ASD patients.[6] Our ASD subjects were categorized as having small ASD (33 subjects; 32%), moderate ASD (35 subjects; 34%) or large ASD (35 subjects; 34%). A previous study reported small ASD in 39 subjects (50%), moderate ASD in 15 (19.23%), and large ASD in 24 (30.77%).[7]

B-type natriuretic peptide is a cardiac neurohormone originating from the granular membrane of the heart ventricles, which contributes to the increase in ventricular volume and blood pressure. On statistical tests, there was significant difference in the average difference in BNP levels in malnourished and poor nourished as well as malnourished and good nourished with the value of P=0.001. Similarly, a previous study reported a correlation in malnourishment and higher BNP levels in children.[8] We found significantly higher mean BNP in the medium ASD group compared to the small ASD group, the large ASD group compared to the small ASD group, as well as the large ASD group compared to the medium ASD group. A study also noted a correlation between BNP level and ASD size.[9] In addition, a study showed higher BNP levels in their ASD group (79 pg/mL) compared to a control group (57 pg/mL) (P<0.05).[10] This shows that BNP levels can match echocardiography in diagnosing the size of ASD.

Bivariate analysis revealed that nutritional status and ASD diameter had significant correlations with BNP level. However, multivariate analysis revealed that only ASD diameter was significantly correlated with BNP level. This finding indicates that using BNP level to estimate ASD size is equivalent to echocardiographic ability, with a regression equation of a 1 mm increase in ASD diameter for a 0.0009 pg/mL BNP increase. Another study stated that serum BNP levels were higher in ASD patients compared to the control group (healthy subject), all of whom had been examined using echocardiography.[7] A previous study likewise found that serum BNP levels were higher in patients with larger ASDs.[8] These studies suggest that BNP levels can be used as a diagnostic tool to predict ASD size.

Some subjects in our study had low BNP levels accompanied by moderate or large ASDs. These low BNP levels may have been due to the absence of adaptation or compensation for the enlargement of the cardiac chamber; the resulting defects also have not shown any significant hemodynamic disorders. In addition, the enlargement of heart space is also influenced by age and nutritional status.[6]

The strength of our study was we determine the cut off point the size of ASD and relation with the BNP levels. Also, echocardiographic results were interpreted by pediatric cardiologists, then validation and reliability were tested in the interpretation of electrocardiogram results. In addition, this study was conducted at Dr. Wahidin Sudirohusodo Hospital, which is a national referral center in Eastern Indonesia, so our results are representative of ASD children in Eastern Indonesia. The limitation of this study was that BNP measurements were only done once.

The application of our study results is that in patients with clinically acyanotic CHD who are suspected of ASD, high BNP level is a strong indicator of moderate-large ASD. Such patients require immediate treatment, so early diagnosis is needed. In addition, BNP levels could also be used to monitor the success of further treatment. Patients with systolic ejection noise, wide-fixed split, and low BNP level are likely to have a small ASD, but such conditions do not rule out the presence of a moderate ASD, so these patients must be urgently referred for echocardiography. Therefore, history-taking, physical examination, and BNP measurements are needed by primary care physicians to be able to diagnose CHD early and determine when patients should be referred immediately to tertiary services.

Conflict of Interest

None declared.

Funding Acknowledgment

The authors received no specific grants from any funding agency in the public, commercial, or not-for-profit sectors.

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