RESEARCH ARTICLE

Journal of Anatolian Medical Research
JAMER 2023;8(4):33-7
DOI:10.55694/jamer.1365421

Galectin-3 in Children with Secundum Atrial Septal Defect

Sekundum ASD'li Çocuklarda Galectin-3

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ÖZET

Amaç: *Pediatrik popülasyonda galektin-3'ün kardiyak biyobelirteç olarak rolüne ilişkin sınırlı sayıda çalışma bulunmaktadır. Sekundum atriyal septal defekti (ASD) olan çocuklarda galektin-3 düzeyini ve bunun B-tip natriüretik peptidinin N-terminal prohormonu (NT-proBNP) ile ilişkisini araştırmayı amaçladık.*

Gereç ve Yöntemler: *Hasta grubunu sekundum ASD'li 27 hasta oluşturdu. Kontrol grubunu benzer yaş ve cinsiyette 30 sağlıklı çocuk oluşturdu. Transtorasik ekokardiyografi ile herhangi bir pencereden ölçülen en büyük ASD çapı ASD boyutu olarak kaydedildi. NT-ProBNP ve galektin-3 için kan örnekleri toplandı.*

Bulgular: *Sekundum ASD'li çocukların NT-ProBNP düzeyleri sağlıklı çocuklara göre anlamlı derecede yüksekti (p=0.003). Sekundum ASD'li çocukların galektin-3 düzeyleri sağlıklı çocuklarla benzerdi (p=0.377). Sekundum ASD'li çocuklarda galektin-3 ile NT-ProBNP düzeyleri arasında istatistiksel olarak önemli pozitif korelasyon mevcuttu (rho=0.454, p=0.017). Galektin-3 eğrisi altında kalan alan istatistiksel olarak anlamlı değildi (AUC=0.537; p=0.643).*

Sonuç: *Sekundum ASD'li hastalarda NT-ProBNP düzeyinde artış olmasına rağmen galektin-3 düzeyinde değişiklik olmadı. NT-ProBNP, sekundum ASD'nin tahmini için değerli bir biyobelirteç olmasına rağmen, galektin-3'ün bu hastalığı öngörmede rolü yoktu.*

Anahtar Kelimeler: *Atriyal septal defekt, galektin-3, B-tip natriüretik peptid, çocuk*

ABSTRACT

Aim: *There is a limited number of studies on the role of galectin-3 as a cardiac biomarker in the pediatric population. We aimed to investigate galectin-3 level and its relationship with N-terminal prohormone of brain natriuretic peptide (NT-proBNP) in children with secundum atrial septal defect (ASD).*

Material and Methods: *Twenty-seven patients with secundum ASD formed the patient group. Thirty healthy children of similar age and gender formed the control group. The largest ASD diameter measured from any window with transthoracic echocardiography was recorded as the ASD size. Blood samples were collected for NT-ProBNP and galectin-3.*

Results: *Children with secundum ASD had significantly higher NT-ProBNP levels compared with the healthy children (p=0.003). Galectin-3 levels of children with secundum ASD were similar to those of the healthy children (p=0.377). There was a statistically positive correlation between galectin-3 and NT-ProBNP levels in children with secundum ASD (rho=0.454, p=0.017). The area under the curve of galectin-3 was not statistically significant (AUC=0.537; p=0.643).*

Conclusion: *Although there was an increase in NT-ProBNP level in patients with secundum ASD, galectin-3 level did not change. Although NT-ProBNP was a valuable biomarker for the prediction of secundum ASD, galectin-3 had no role in predicting this disease.*

Keywords: *Atrial septal defect, galectin-3, brain natriuretic peptide, child*

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Cite this article as: Özkul F, Argun M, Sunkak S, Koçer D. Galectin-3 in Children with Secundum ASD. JAMER 2023;8(4)33-7.

Received: 24.10.2023
Accepted: 31.10.2023
Online Published: 05.12.2023

INTRODUCTION

Atrial septal defects (ASD) are one of the most common congenital heart diseases (CHD). Secundum ASD, the most commonly seen ASD type, results from a tissue defect at the level of fossa ovalis. Although most children with this defect appear asymptomatic, tachypnea, exercise intole, slowed weight gain, and frequently recurring lower respiratory tract infections are seen particularly in cases with a large defect (1,2). The degree of shunt in secundum ASD is dependent on defect size and also atrial pressures which is related to left and right ventricular compliances. Excess volume overload on right heart, which is dominant initially, and then pressure overload, cause leftward interventricular septum deviation, and reduced left ventricular compliance via adverse interventricular interaction. These changes results in reduced left ventricular diastolic filling and systemic output. All these processes take place myocardial cell hypertrophy and fibrosis as well as a series of changes in pulmonary vasculature (1).

Galectin-3 is a new biomarker generally known as a marker of inflammation, cardiac remodeling, and fibrosis. Galectin-3 protein is a member of beta-galactosidase binding galectin protein family and includes a carbohydrate recognition site. Galectin-3 is a chimera-type galectin having a single carbohydrate recognition site bound to an N-terminal site. Galectin-3 is produced and released by many cells. Galectin-3 is involved in many possible mechanisms in the pathophysiology of heart failure, including inflammation, fibrosis, remodeling, apoptosis, and inhibition of antioxidation (3). A biomarker of myocardial fibrosis, galectin-3 not only predicts hospitalization and death, but also contributes to the prognostic value of the natriuretic peptides in adult patients with heart failure. American College of Cardiology/American Heart Association 2013 Heart Failure Management Guidelines recommend the use of galectin-3 for predicting prognosis in addition to risk stratification (class IIb) (4). The current European Society of Cardiology heart failure management guidelines, on the other hand, do not recommend the use of galectin-3 in clinical practice (5).

There is a limited number of studies in the literature on the role of galectin-3 as a cardiac biomarker in the pediatric population. We aimed to study galectin-3 level and its relationship with NT-ProBNP in children with secundum ASD.

MATERIAL and METHODS

Ethical Approval and Consent to Participate

This study was conducted at Health Sciences University Kayseri Medical Faculty, Kayseri City Training and Research Hospital Department of Pediatrics between June 2020 and January 2021. It was approved by Kayseri City Hospital Clinical Research Ethics Committee (April/2020, no.43). The families of all children in the patient and control groups were informed and gave informed consent.

Subjects

Twenty-seven pediatric patients diagnosed with secundum ASD by the same pediatric cardiologist at Kayseri City Training and Research Hospital, Pediatric Cardiology Outpatient Clinic formed the patient group. Thirty healthy children of similar age and gender formed the control group.

Exclusion criteria**:** Patients with a small secundum ASD, another cardiac pathology accompanying ASD, and comorbidities causing nutritional problems such as infection, chronic disorders, syndrome, cleft lip-palate were excluded from the study.

Echocardiography

The transthoracic echocardiographic examinations of the children were performed by the same pediatric cardiologist using a Vivid Pro7 (GE, Vingmed Ultrasond, Horten, Norway) echocardiography device and 2-dimensional, color Doppler, CW Doppler, and M mode echocardiographic examinations. The largest ASD diameter measured from any window was recorded as the ASD size. The ASD diameter/body surface area (BSA) ratio was calculated using the largest measured ASD diameter divided by the child's BSA. A large secundum ASD was defined as a defect with an ASD size/BSA ratio equal to or greater than 15 mm/m^2. Moderate secundum ASD was defined as a defect larger than 7 mm and an ASD size/BSA ratio less than 15 mm/m^2 (6).

Cardiac Biomarkers

For complete blood count, 2 cc blood samples were taken into a tube containing ethylenediamine tetraacetic acid. Blood samples were studied on the same day with a Sysmex brand-ed XN-9000 model device.

The 2 cc blood samples taken for NT-ProBNP measurement were centrifuged to separate their sera. NT-ProBNP measurements were performed according to standard procedures using sandwich enzyme-linked immuno-sorbent assay method developed by Roche Diagnostics (Elecsys® pro-BNP II, Cobas, Mannheim, Germany). The analytical sensitivity of the kit is 5 pg/mL, assay range 5-35000 pg/mL.

Serum samples of the patient and control groups were stored at -80°C until the day of analysis. According to the manufacturer's instructions, serum galectin-3 levels were studied by sandwich enzyme-linked immuno-sorbent assay method using a commercial kit (Cloud-Clone Corp, TX, USA). The galectin-3 level was expressed as ng/mL. Detection range for serum galectin-3 are 0.156-10 ng/mL. For all parameters, the concentrations of the samples were calculated using calibration curves obtained from study standards with known levels.

Statistical Analysis

Study data were analyzed using IBM SPSS Statistics 26.0 (IBM Corp. Armonk, New York, ABD) statist software package. Descriptive statistics were presented as n, % for categorical variables, and mean ± standard deviation (min-max) or median and interquartile range for continuous variables, depending on the normality of their distribution. Normality of distribution of continuous variables by study groups was tested with Shapiro Wilk test. Homogeneity of variances of continuous variables by study groups was tested with Levene test. Independent samples t test was performed to compare the distribution of galectin-3 by the patient and control groups. Mann Whitney U test was performed to compare NT-ProBNP between the patient and control groups. Spearman correlation test was performed to examine the relationship between NT-ProBNP and galectin-3 variables. Receiver operating characteristics curve analysis was performed to test the abilities of NT-ProBNP and galectin-3 to predict heart failure and to determine their cut-off points for diagnostic statistics. The area under the curve was calculated for each of the two variables.

RESULTS

Twenty-seven patients with secundum ASD (18 females, 9 males) (p=0.315) had a median age of 24 months and 30 healthy children (15 females, 15 males) had a median age of 13.5 months (p=0.892), with no statistically significant difference. The number of patients with large ASD was 20. Eight of those patients had been treated with enalapril for heart failure for at least 6 months. The number of patients with moderate ASD was 7. There was no significant difference between the median (interquartile range) body weight [11(7) kg] and z score (mean ± SD; -0.45±1.72) of the children with secundum ASD and the median (interquartile range) body weight [9.9 (18.65) kg] and z score (-0.20±1.29) of the healthy children (p=0.527 for z score). There was no significant difference between the median (interquartile range) height [85 (33) cm] and z score (mean ± SD; -0.17±1.42) of the children with secundum ASD and the median (interquartile range) height [81.5 (61) cm] and z score (0.07±1.62) of the healthy children (p=0.560 for z score).

Children with secundum ASD had a significantly higher NT-ProBNP level than the healthy children. Children with secundum ASD had a statistically similar galectin-3 level with healthy children (Table 1).
Patients with a large ASD treated with enalapril had statistically similar NT-ProBNP and galectin-3 levels with patients having a large ASD who were not treated for heart failure (Table 2).

There was a positive correlation between galectin-3 and NT-ProBNP in children with secundum ASD (rho=0.454, p=0.017). NT-ProBNP had a statistically significant area under the curve for predicting secundum ASD (AUC=0.731; p<0.001). The optimum cut-off point for NT-ProBNP was determined as >157.3 ng/L, for which the sensitivity was 55.6%, specificity 83.3%, positive predictive value 75.0%, and negative predictive value 67.6%. The area under the curve for galectin-3 was not statistically significant (AUC=0.537; p=0.643) (Table 3).

Table 1. N-terminal prohormone of brain natriuretic peptide and galectin-3 levels of children with secundum atrial septal defect and healthy children.

	Groups			
Variables	**Secundum ASD (n=27)**	**Healthy (n=30)**	**Test Statistics**	**p value**
NT-ProBNP (pg/mL) M (IQR)	163.80 (189.69)	82.64 (93.76)	-2.997	0.003+
Galectin-3 (ng/mL)	1.78±0.55	1.98±1.13	-0.893	0.377*
Mean±SD (Min-Max)	(0.12-2.88)	(0.18-5.20)		

ASD: atrial septal defect, ***NT-ProBNP:*** N-terminal prohormone of brain natriuretic peptide, ***M:*** Median; IQR: Interquartile range; Mean ± SD: mean ± standard deviation, +Mann Whitney U test; *Independent samples t test

DISCUSSION

We determined that although NT-ProBNP was high, galectin-3 did not change in children with secundum ASD. However, there was a positive correlation between galectin-3 and NT-ProBNP.

It was proven that galectin-3 is an important prognostic tool as a cardiac biomarker in adults. However, it has not been determined as a biomarker in daily clinical practice in pediatric heart disease. Nevertheless, there are studies on galectin-3 as a biomarker in cardiac disorders in children. Although the evidence is based on small cohort studies, it is stated that galectin-3 could serve as a potential biomarker in cardiovascular risk stratification in heart failure patients (3).

Table 2. Comparison of the NT-proBNP and galectin-3 variables in patients with large ASD by the status of receiving drug treatment for heart failure

	Groups			
Variables	**Receiving Heart Failure Treatment (n=8)**	**Not Receiving Heart Failure Treatment (n=12)**	**Test Statistics**	**p value**
NT-ProBNP (pg/mL) M (IQR)	218.20 (246.95)	187.50 (174.20)	-0.926	0.384+
Galectin-3 (ng/mL)	1.84±0.49	1.87±0.51	-0.1 35	0.894*
Mean±SD (Min-Max)	(1.24-2.53)	(1.07-2.88)		

ASD: atrial septal defect, ***NT-ProBNP:*** N-terminal prohormone of brain natriuretic peptide, ***M:*** Median; ***IQR:*** Interquartile range; Mean ± SD:

Table 3. Receiver operating characteristics curve analysis of the predictive abilities of the N-terminal prohormone of brain natriuretic peptide and galectin-3 variables for secundum atrial septal defect.

Variables	**Cut-off**	**AUC**	**95% CI**	**p value**	**Sens**	**Spec**	**PPV**	**NPV**	**LR+**	**LR-**
NT-ProBNP (pg/mL) M (IQR)	> 157.3	0.731	0.598-0.840	<0.001	55.60	83.30	75.0	67.6	3.33	0.53
Galectin-3 (ng/mL)	>0.95	0.537	0.400-0.670	0.643	3.70	73.30	11.1	45.8	0.14	1.31

NT-ProBNP: N-terminal prohormone of brain natriuretic peptide; Cut-off: Cut-off point; ***AUC:*** Area under the curve, 95% CI: 95% Confidence interval, ***Sens:*** Sensitivity, ***Spec:*** Specificity; ***PPV:*** Positive predictive value, ***NPV:*** Negative predictive value, ***LR+:*** Positive likelihood ratio, ***LR-:*** Negative likelihood ratio

Baggen VJM, et al. (6) found galectin-3 significantly correlated to functional capacity, cardiac function, and adverse cardiovascular events in 591 adults with CHD. However, the contribution of galectin-3 to N-terminal prohormone of brain natriuretic peptide, a more traditional risk marker, was limited.

A study that analyzed the preoperative and postoperative levels of new biomarkers after pediatric congenital heart surgery revealed that preoperative galectin-3 were strong and significant predictors for readmission and/or mortality in 145 pediatric patients that underwent congenital heart surgery (7).

Saleh N, et al. (8) reported an increase in galectin-3 level in children with CHD. The increase in galectin-3 level was more prominent in patients with heart failure symptoms and reduced ejection fraction. Galectin-3 level showed a positive correlation with the Ross classification and a negative one with ejection fraction. However, they detected no significant correlation between galectin-3 level and heart failure mortality.

Kotby AA, et al. (9) reported that galectin-3 is increased in children with heart failure and that increase was positively correlated to Ross heart failure classification. Galectin-3 level was markedly lower in patients taking sprinolactone. Elhewala AAS. et. al. (10) reported that galectin-3 level was increased and showed a positive correlation with the Ross heart failure classification in children with heart failure due to CHD. Cura C. et al. (11) reported that galectin-3 increased independently from left ventricular dilation in infants with ventricular septal defect and showed that it had a biomarker characteristic of similar power with NT-ProBNP in predicting the disease. Muhammed LA. et al. (12) reported that among children with CHD, galectin-3 was higher in children with HF than those without, and also that galectin-3 was correlated to left atrial and left ventricular diameters.

Frank BS, et al. (13) examined the relationship between galectin-3 and persistent echocardiographic left ventricular abnormalities during mid-term follow-up in patients with coarctation of the aorta undergoing surgical repair. Preope rative galectin-3 level was higher in the newborns than older children. There was no linear relationship between galectin-3 and left ventricular mass index at preoperative period or during the follow-up period. Galectin-3 did not change from the preoperative period to the postoperative period.

Zegelbone PM, et al. (14) showed no correlation between galectin-3 and the hemodynamic indices of right heart volume and pressure overload resulting from pulmonary valve insufficiency and/or stenosis prior to pulmonary valve replacement. van den Bosch E. et al. (15) reported a correlation between NT-ProBNP and late-term outcomes but no correlation between galectin-3 and cardiac function or long-term outcomes in patients who underwent Fontan procedure. Galectin-3 had no potential in risk stratification of patients who had undergone the Fontan procedure.

It is known that activated renin-angiotensin-aldosterone system, sympathetic nervous system, and inflammation activate galectin-3 and this effectively promote cardiac remodeling and fibrosis. We believe that the absence of galectin-3 increase in our secundum ASD patients can be explained by the absence of the signs and symptoms of heart failure. Galectin-3 level of patients who were under enalapril treatment was similar to that who were not treated with the drug. However, due to the small number of cases, it seems difficult to interpret the effect of this treatment on galectin-3 levels.

Limitations: First of all, the small number of patients and thus in the groups is a study limitation. Second limitation is the absence of any measurement of dilated right atrial and right ventricular diameters in secundum ASD. Thirdly, the absence of the measurement of invasive hemodynamic parameters may be a limitation. Fourthly, the absence of any comparison between pretreatment and posttreatment values in the treated group is also a limitation.

Conclusion

In our study, where galectin-3 levels were analyzed in patients with secundum ASD for the first time, NT-ProBNP level was found to increase although galectin-3 level did not change. Although NT-ProBNP is a valuable biomarker for predicting secundum ASD, galectin-3 had no role in the prediction of this disease. Shunt level being at atrial level and the absence of the signs and symptoms of heart failure in secundum ASD may explain the absence of any change in galectin-3 level. We found evidence supporting our hypothesis that the mechanisms increasing galectin-3 are related to the systems activated in heart failure and inflammation rather than ventricular dilatation.

Ethics Committee Approval: This study was approved by Kayseri City Hospital Clinical Research Ethics Committee (April/2020,no.43).

Conflict of Interest: The authors declare no conflict of interest in this study.

Financial Disclosure: No financial support was received from any institution or organization for this study.

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