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Predictors of Spontaneous Closure of Atrial Septal Defect and Ventricular Septal Defect in Children

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ABSTRACT

Background: Ventricular septal deformity (VSD) and Atrial septal deformity (ASD) are the most common congenital heart disease (CHD). This study intended to help improving morbidity and mortality of pediatrics patient with Ventricular septal defect and ASDs, through achieving the following objectives; assessment the role of diameter of defect, child age, measurement of serum l.carnitine and phospholipids in early spontaneous closure of atrial septal defects and ventricular septal defects . **Patients and Methods:** This was a cohort study was carried out at Pediatric Cardiology Unit of Zagazig University hospitals during the period from October 2019 to October 2020 Included 30 children up to 2 years of age were following for ASD or VSD. The patients were categorized into 2 groups: Group I; comprised 20 patients with ASD. Group II; comprised 10 patients with VSD were observed for 12 months with successive 2-dimensional echocardiography. All patients were subjected to full history and examination with special focus on cardiac manifestations, follow up echocardiography at 3 and 6 months viewing extent of the deformities which compared to preceding echocardiographic reports. Laboratory investigations was done with detection of Lcarnitine and phospholipids levels. **Results**: There was statistically significant higher total phospholipid among ASD patients with natural closure than regression to ≤ 3 mm and than residual >3 mm **(**p-value = 0.001) with no statistically significant difference regarding L. Carnitine (p-value = 0.1). There was statistically significant higher L. Carnitine among th e VSD patients with regression to ≤ 3 mm than residual >3 mm (p-value =0.01) with no statistically significant difference regarding total phospholipid (p-value =0.1). Age at diagnosis, defect size, total phospholipids and L-Carnitine were the statistically significant predictor factors for spontaneous closure of ASD and VSD among the studied group, **Conclusion**: Age at diagnosis, defect size, total phospholipids and L-Carnitine were the statistically significant predictor factors for spontaneous closure of ASD and VSD among the studied group.

Keywords: Ventricular septal deformity , Atrial septal deformity , L. Carnitine, echocardiography , natural closure.

INTRODUCTION

ASD is one of the most frequently noticed congenital heart diseases. Children are nowadays directed to centers of pediatric cardiology at an earlier age, which has reduced mean discovery age for ASD to 6 months [**1].**

Asymptomatic Atrial Septal Deformities (ASD) are possibly closed when the kids have got the age of 3–5 years. A significant ASD causes a left to right by-pass causing capacity overload, expansion of the right atrium and ventricle and changed myocardial structure and function. Preterm kids may be three times as common between kids with percutaneous method closure than in the overall population [**2**].

The myocardium of the preterm kid has permanent morphological and total structural changes. Even long after the neonatal period and into later life, the morphology of both the ventricles as well as the role is decreased or changed. Improvements in perinatal care over the previous 30 years have led to important improvements in survival rates, but the hazard of early death and pulmonary, neurological, cognitive and cardiovascular morbidity remains [**3**].

Ventricular septal defect (VSD) is the most public congenital heart deformity, which occuring in 20%-42.86% of all congenital heart deformities (CHD). The occurrence of VSD is around 1.35 to 17.3 per 1000 live births. Some of these deformities can close naturally, or reduce without surgical involvement [**4].**

However, some patients will suffer from difficulties such as growth delay, frequent infections, congestive heart failure, and even unexpected death. Therefore, it is very significant for pediatricians to select whether the children with VSD require surgical involvements, and even more significantly, when these interferences should be done. A few new studies have studied the prognosis associated features in patients with VSD [**5]**.

Features such as magnitude and site of the deformities, ages of diagnosis, and the occurrence of membranous septal aneurysm have been known as predictors of natural closure. In addition, ratio of VSD area to body surface area, ratio among size of the defect to aortic root diameter (D VSD/DAR), shunt ratio (Qp/Qs), as well as comorbidities of congestive heart failure (HF) have also been assessed[**6]**.

New studies have informed that the phospholipids and the L-carnitine levels have a valued and significant role in the pathogenesis and prognosis of congenital heart illness with right or left ventricular capacity or pressure overload as in ASD, VSD or PDA. Cell-specific targeting of L-carnitine and phospholipid biosynthetic pathways could work for a significant approach for helping in treatment of congenital heart illnesses [**7].** Carnitine depletion, characterized by reduced expression of "organic cation transporter-2" gene, is a metabolic and autosomal recessive disorder that also commonly relates to CVD. Hence, exogenous carnitine administration through dietary and intravenous paths aids as a appropriate protective approach against ventricular dysfunction, ischemia-reperfusion injury, cardiac arrhythmia and toxic myocardial damage that obviously mark CVD. Moreover, carnitine decreases hypertension, hyperlipidemia, diabetic ketoacidosis, hyperglycemia, insulin-dependent diabetes mellitus, insulin resistance, obesity, etc. that progress cardiovascular pathology. These favorable properties of l-carnitine have been obvious in infants, juvenile, young, adult and aged patients of unexpected and chronic heart failure as well [8]. Phospholipids are fundamental normal parts of the cell membrane, regulating the cell membrane task, and intercellular links. Clinically, the serum total phospholipids level is showed to be a liver and biliary illnesses marker. Lately, it has been accounted that phospholipids and phospholipid hydrolysates assume vital parts in bioactivity as lipid mediators and in atherosclerosis development from dyslipidemia [9].

This study intended to know the role of size of deformity, kid age, l.carnitine and phospholipids in early natural closure of atrial septal deformities and ventricular septal deformities.

PATIENTS AND METHODS

This cohort study was done at Pediatric Cardiology Unit of Zagazig University hospitals during the period from October 2019 to October 2020 Included 30 children up to 2 years of age who were following for ASD or VSD. The patients were categorized to 2 groups: Group I; comprised 20 patients with ASD. Group II; comprised 10 patients with VSD

Inclusion criteria: All kids up to 2 years of age who were following for ASDs and VSDs progress by echocardiography in Zagazig University Hospitals. **Exclusion criteria:** Kids with electrolyte imbalance, cancer, hepatic or kidney illness. Kids with aortic stenosis, moderate or severe regurgitation of the mitral or tricuspid valves, pulmonary stenosis, Eisenmenger syndrome.

Written known agreement was taken from the patient parents to join in the study. The agreement for the study was received from the Pediatrics Departments of Zagazig University Hospitals after the agreement of the Institutional Review Board (IRB). The research was done in compliance with the Code of Ethics of the World Medical Association (Decleration of Helsinki) for studies including humans.

METHODS

Each Patient is exposed to complete history taking containing Prenatal history, Natal history; gender, gestational age, weight, invasive approach as (blood transfusion, endotracheal intubation and mechanical ventilation). Full History for nature of feeding, iron supplementation, L.carnitine and Vitamin D. Full clinical check; general reflexes , vital signs , systemic investigation including neurological, respiratory, cardiovascular, abdominal …etc. Follow up echocardiography at 3 and 6 months from enrollment of the study viewing extent of the deformities which compared to preceding echocardiographic reports. Examination by Transthoracic echocardiogram, the probe is sited on the chest or abdomen of the subject to develop several views of the heart. Measurement of serum L.carnitine and total phospholipids and do complete blood cell count.

Total Phospholipids

Serum, Heparinized plasma or EDTA plasma. Serum can be kept for up to 7 days at +2 to +8°C and 2 days at +15 to +25°C. Below complete aseptic situation, 5 ml of venous blood were withdrawn from each subject after an overnight fasting and separated into 2 parts. The first part 2.5 ml was transported into a plain tube, left at37ºC for 30 min to clot then centrifuged for 10 min at 4000 r.p.m. The serum got was placed into aliquots and saved in -80°C untill time of study for determination of marker serum level (Normal range(100 – 275) mg/dL).

Human total carnitine (TC)ELISA Kit

Below full aseptic situation, 5 ml of venous blood were withdrawn from each subject after an overnight fasting and separated into 2 parts. The first part 2.5 ml was transported into a plain tube, left at37ºC for 30 min to clot then centrifuged for 10 min at 4000 r.p.m. The serum got was placed into aliquots and saved in -80°C untill time of study for determination of marker serum level using ELISA (Normal range(28-62) µmol/L)

The kit procedures a double-antibody sandwich enzyme-linked immunosorbent assay (ELISA) to assess the level of Human total carnitine (TC) in samples. Add total carnitine (TC)to monoclonal antibody Enzyme well which is pre-coated with Human total carnitine (TC) monoclonal antibody, incubation; then, add (TC)antibodies labeled with biotin, and united with Streptavidin-HRP to form immune complex; then do incubation and washing again to remove the uncombined enzyme. Then add Chromogen Solution A, B, the color of the liquid alters into the blue and at the influence of acid, the color lastly develops yellow. The chroma of color and the concentration of the Human Substance total carnitine (TC) of sample were definitely associated.

STATISTICAL ANALYSIS

Data were checked, entered and studied using SPSS version 23 for data processing. Data were expressed as number and percentage for qualitative variables and mean + standard deviation (SD) for quantitative one. The evaluation was carreied out using: Chi- square test (X2), ANOVA (F-test) test, Linear regression analysis, the threshold of significance was fixed at 5% level (P-value).

RESULTS

There was statistically important difference among the ASD &VSD patients regarding age at diagnosis with higher age between ASD than VSD group. But concerning body weight, weight percentile, body surface area, sex distribution, consanguinity, feeding and mode of delivery, there was no statistically important difference among the ASD &VSD patients **(Table 1).**

There was no statistically important difference among ASD &VSD patients concerning illness period, occurrence of chest illnesses, heart failure, drug history and deformity magnitude at diagnosis **(Table 2)**.

This study revealed that there was statistically important higher L. Carnitine and total phospholipid between ASD than VSD patients **(Table 3)**.

This study revealed that there was statistically important reduction on the ASD size after the follow up. But concerning VSD, the deformity diameter was enlarged after the follow up with no statistical importance **(Table 4).**

This study revealed that there was statistically important difference in the result between patients with dissimilar deformity nature, (60.0%) of the ASD had natural closure (5.0%) reduced to ≤ 3 mm and (35.0%) residue to more than 3 mm while (70.0%) of VSD residue to more than 3 mm and 30 % of VSD reduced to ≤ 3 mm.

That there was statistically important higher total phospholipid between the ASD patients with natural closure than reducing to ≤ 3 ml than residual >3 ml with no statistically important difference concerning L. Carnitine **Table (5).**

This study shows that there was statistically significant higher total phospholipid among the ASD patients with spontaneous closure than regression to ≤ 3 ml than residual >3 ml with no statistically significant difference regarding L. Carnitine **(Table 6)**.

This revealed that there was statistically important higher L. Carnitine between the VSD patients with decreasing to ≤ 3 ml than residual >3 ml with no statistically important difference regarding total phospholipid. This study revealed that age at diagnosis, deformity diameter, total phospholipids and L-Carnitine were statistically important predictor influences for natural closure of ASD and VSD between the studied group. **(Table 7).**

Table (1): Comparing socio-demographic data among the different defect lesions:-

Variables	*ASD (NO=20)* mean ± SD	*VSD (NO=10)* mean ± SD	t- test	p-value
Age (months)	12.4±4.1	18.5±5.7	3.3	**0.002***
Weight (kg)	9.5±1.3	9.8±1.9	0.4	0.6
Weight percentile	55.3±26.6	43.2±34.6	M.W 1.1	0.3
Body surface area	0.43±0.02	0.44±0.06	0.4	0.6
Variables	***ASD NO (%)***	***VSD NO (%)***	**χ^2**	**p-value**
Gender				
Male	8 (40.0%)	7 (70.0%)		
Female	12 (60.0%)	3 (30.0%)	FET	0.2
Mode of delivery				
Vaginal	2 (10.0%)	1 (10.0%)	FET	1
C.S	18 (90.0%)	9 (90.0%)		
Order of kid				
1ST	3 (15.0%)	1 (10.0%)		
2nd	10 (50.0%)	5 (50.0%)		
3rd	6 (30.0%)	2 (20.0%)	2.6	0.6
4th	1 (5.0%)	1 (10.0%)		
5th	0.0 (00.0%)	1 (10.0%)		
Feeding				
Breast feeding	11 (55.0%)	4(40.0%)	0.6	0.7
Artificial	9 (45.0%)	6 (60.0%)		
Consanguinity				
Present	2 (10.0%)	1(10.0%)	FET	1
Absent	18 (90.0%)	9 (90.0%)		

*Statistically significant difference ($P \leq 0.05$)
M.W=Mann-Witenny U test.

Table (2): Comparing clinical data among the different defect lesions:-

Variables	*ASD (NO=20)* mean ± SD Median	*VSD (NO=10)* mean ± SD Median	M.W test	p-value
Disease duration *(days)*	41.3±38.9 29	25.5±22.9 15.0	1.2	0.2
Variables	***ASD NO (%)***	***VSD NO (%)***	**χ^2**	**p-value**
Presence of chest diseases	14 (70.0%)	8 (80.0%)		
Recurrent chest infection	6 (30.0%)	2 (20.0%)	FET	0.7
And respiratory distress				
Heart failure				
Yes	4 (20.0%)	4 (40.0%)	1.3	0.2
No	16 (80.0%)	6 (60.0%)		
Drug history				

Variables	*ASD (NO=20)* mean ± SD Median	*VSD (NO=10)* mean ± SD Median	M.W test	p-value
No	12 (60.0%)	2(20.0%)		
Lanoxin	4 (20.0%)	4 (40.0%)	8.1	0.1
Lasix&capotin	5 (25.0%)	6 (60.0%)		
Lasix	2 (10.0%)	1 (10.0%)		
Capotin	0.0 (00.0%)	1 (10.0%)		
Defect size at diagnosis				
≤ 5 mm	15 (75.0%)	5 (50.0%)	1.8	0.2
>5 mm	5 (25.0%)	5 (50.0%)		

Table (3): Comparing L. Carnitine and total phospholipids among the different defect lesions:-

Variables	*ASD (NO=20)* mean ± SD median	*VSD (NO=10)* mean ± SD median	test	p-value
L. Carnitine *(pg/ml)*	1.3±0.7 1.74	0.4±0.3 0.17	M.W= 3.5	**0.001****
Total phospholipids *(mg/ml)*	217.4±79.3 220.7	152.9±49.2 127.8	T= 2.3	**0.02***

*Statistically significant difference (P ≤ 0.05),**Statistically highly significant difference (P ≤ 0.001), M.W=Mann-Witenny U test, T= t-independent test.

Table (4): Comparing defect size at diagnosis and after the follow up among the different defect lesions:-

Variables	Defect size *At diagnosis*	Defect size *After follow up*	W.S.R test	p-value
ASD				
mean ± SD	4.45±2.01	2.32±1.4	3.6	**0.03***
Median	4	2		
VSD	4.92±3.2			
mean ± SD	3.6	5.2±3.1		
Median		4.25	2.1	0.1

W.S.R=Wilcoxon Signed Rank test.

Table (5): Relation between the defect type and its outcome among the studied group:-

The defect	*Spontaneous closure NO. (%)*	*Regress to ≤ 3 mm NO. (%)*	*Residual to > 3 mm NO. (%)*	χ^2	p-value
ASD (20)	12 (60.0%)	1 (5.0%)	7 (35.0%)	10.8	**0.004***
VSD (10)	0.0 (0.0%)	3 (30.0%)	7 (70.0%)		

*Statistically significant difference (P ≤ 0.05)

Table (6): Comparing L. Carnitine and total phospholipids between ASD patients with different outcome among the studied group:-

Variables	*Spontaneous closure* (NO.=12)	*Regress to ≤ 3 mm* (NO.=1)	*Residual to > 3 mm* (NO.=7)	F test	p-value
L. Carnitine *(pg/ml)* mean ± SD	1.54±0.5	0.19±.04	1.11±0.08	2.4	0.1
Total phospholipids *(mg/ml)* ***mean ± SD***	257.4±67.1	266.2±53	141.8±37.8	9.1	**0.002***

F-test=ANOVA test, *Statistically significant difference (P ≤ 0.05)

Table (7): Comparing L. Carnitine and total phospholipids between VSD patients with different outcome among the studied group:-

Variables	*Regress to ≤ 3 mm* (NO.=3)	*Residual to > 3 mm* (NO.=7)	M.W test	p-value
L. Carnitine *(pg/ml)* mean ± SD	0.98±0.7	0.16±0.19	3.1	**0.01***
Total phospholipids *(mg/ml)* ***mean ± SD***	186.2±74.9	138.7±31.2	1.5	0.1
Variables	**Regression coefficient**	***p***	***95% C.I***	
Age at diagnosis	0.8	**0.03***	*(0.1-0.3)*	
Weight percentile	0.1	0.7	*(0.2-1.04)*	
Body surface area	0.5	0.20	*(0.98-1.06)*	
Defect size at diagnosis	1.7	**0.002***	*(0.3-0.9)*	
LPA(mm)	0.5	0.20	*(0.58-2.4)*	
AO(mm)	0.1	0.07	***(0.1-12.0)***	
Total phospholipids	**3.5**	**0.03***	***(0.08-0.6)***	
L-Carnitine	**0.8**	**0.04***	***(1.4-13.1)***	
	ANOVA=2.7 ,p-value=0.01* R2=0.7 Durbin Watson=1.6			

M.W =Man Witenny test, *Statistically significant difference (P ≤ 0.05)
*Statistically significant difference (P ≤ 0.05)

DISCUSSION

Atrial septal defect (ASD) is a common congenital disorder with a prevalence of approximately 2 per 1,000 live births.There is four types of ASDs: secundum, primum, sinus venosus, and coronary sinus. Secundum ASDs are the most common, making up more than 70% of all ASDs**[10].**

Ventricular septal defect (VSD) is the most common congenital heart defect, which accounts for 20%-42.86% of all congenital heart diseases (CHD). The incidence of VSD is approximately 1.35 to 17.3 per 1000 live births. Some of these defects can close spontaneously, or diminish without surgical intervention **[4].**

The significant decrease in L-carnitine plasma level in patients may result in improper cardiac metabolism that may lead to cardiomyopathy later. . These compositional changes in the phospholipid profile are similar to that reported by Hamplová et al.2004 They noticed that reduction in the total phospholipids (PL),there was reduction in the total phospholipids (PL), phosphatidylcholine and phosphatidylethanolamine in children with CHD. Interestingly, they found that increase in the total phospholipid level in cyanotic heart disease cases**. [11].**

Our result show that there was statistically important difference among the ASD &VSD patients regarding age at diagnosis with higher age between ASD than VSD group. But concerning body weight, body percentile, body surface area, sex distribution, consanguinity, feeding and mode of delivery, there was no statistically important difference among the ASD &VSD patients.

This were maintained by study of **Özçeker et al. [12]** as they discovered that natural closure of ASD was detected in 58.9% of patients diagnosed among 1 month and 24 months of age and in 33.3% of patients whose ASD was diagnosed when they were 25–60 months of age. In only 3.3% of patients older than 61 months was natural closure noted. A statistically important difference was found between the 3 groups regarding natural closure.

In the study of **Behjati-Ardakani et al. [13]** the median age of the patients with natural closure was 2.25 years, and the maximum age at natural closure was 3.9 years. Their study established previous reports [**13**] demonstrating that natural closure can happen beyond infancy. Therefore, the window of chance for selective surgery can be determined regarding patient age. None of their patients with an ASD size of 9 mm or less required surgery. In their study, 72.4% of patients required surgery or trans catheter closure. However, in their study, 8 (4.1%) cases of natural closure of 9 mm ASDs happened in childhood.

This study revealed that age at diagnosis, deformity diameter, total phospholipids and L-Carnitine were statistically important predictor influences for natural closure of ASD and VSD between the studied group.

Hanslik et al. [14] discovered atrial septal deformity size and age at diagnosis were independent prognosticators of natural closure or decreasing to ≤3-mm deformity diameter. Of atrial septal deformities with a size of 4 to 5 mm at diagnosis, 56% revealed natural closure, 30% decreased to a size of ≤3 mm, and none required surgical closure. Of atrial septal deformities with a size of >10 mm at diagnosis, none closed naturally, whereas 77% needed surgical or device closure. Sex and observation time were not related to natural atrial septal deformity closure or reducing to ≤3 mm.

However, in the study of **Xu et al., [15]** four hundred and twenty-five patients, of which 258 (60.7%) were boys and 167 (39.3%) were girls, were involved in the studies. They were less than six-month-old, weight mean ± SD was 4.3 ± 0.6 kg. The size of VSD was 2.96 ± 1.37 m at natural closure group and was 7.23 ± 1.39 ml in non-spontaneous closure group. There was highly statistically important difference between both groups.

Furthermore, in a study by **Ertürk et al. [16]** 90% of deformities with size of 8mm or more required surgical closure approaches.

Demir et al. [17] reported a natural closure rate of 7.5% in 8 mm ASDs. Overall, it can be determined that natural closure may happen rarely in ASDs measuring 8 - 9 mm.

There was statistically important difference in the result among patients with dissimilar deformity kind, (60.0%) of the ASD had natural closure (5.0%) decreased to ≤ 3 ml and (35.0%) residue to more than 3 ml while (70.0%) of VSD residue to more than 3 ml. There was statistically important reduction on the ASD size after the follow up. But regarding VSD, the deformity diameter was enlarged after the follow up with no statistical importance.

Regarding to **Özçeker et al. [18]**, in only 6 of the 67 cases of ASD with diameter of ≥9 mm was natural deformity closure detected. The remaining 61 cases needed surgery (n=19; 28.4%), or use of transcatheter occlusion technique (n=34; 50.7%) to close the deformity. No patient in the group (n=213) with deformity size among 3 and 5 mm required closure approach, and deformities of 152 (71.4%) patients in this group closed naturally. Natural closure also happened in 31 patients (41.9%) with deformity size of 6–8 mm. A statistically important intergroup difference was revealed regarding deformity size and natural closure of deformity ($p<0.001$).

The current study revealed that There was statistically important higher L. Carnitine between the patients with natural closure than reducing to ≤ 3 ml than residual >3 ml, the statistically important difference was mainly among natural closure and the other groups. Although the reduction to ≤ 3 ml had higher L. Carnitine level than residual >3 ml, this difference wasn't statistically important. There was statistically important higher total phospholipid between the

patients with natural closure than reduction to ≤ 3 ml than residual >3 ml.

This study were maintained by study of **Farouk et al. [19]** as they informed that CHD children had a important low plasma L-carnitine level other than the control group (3.8±1.7pg/ml). Also, there was low plasma L-carnitine level between kids with VSD(1.3±0.7pg/ml) other than those with ASD(1.6±0.5pg/ml) and PDA(1.4±0.6pg/ml), p value < 0.001for all. It was observed that there is a obvious reduction in the plasma lecithin, cephalin, sphingomyelin and other phospholipids levels in CHD cases in contrast to normal kids (p value <0.001). Also, marked variations in the phospholipid profile were detected. There was a important reduction in lecithin levels in CHD group in contrast to normal kids (p value <0.001). The lecithin/cephalin ratio for the control group was 5.62, for ASD was 2.77 and for VSD was 3.19 **[19].**

Farouk et al. [19] established that the findings of this study show that the phospholipids and the L-carnitine levels have a valued and significant role in the pathogenesis and prognosis of congenital heart illness with right or left ventricular size or pressure overload as in ASD or VSD. Cell-specific targeting of L-carnitine and phospholipid biosynthetic paths could help as a potential strategy for helping in treatment of congenital heart illnesses.

In the study of **Lee et al. [20]** ASOs (Atrial septal openings) happen at a relatively high occurrence in VLBW (very low birth weight) infants, but greatest of these close naturally within 3 years.

CONCLUSION

Age at diagnosis, deformity diameter, total phospholipids and L-Carnitine were the statistically important prognosticator factors for natural closure of ASD and VSD between the studied group. On the basis of this information, parents can be learned about the prognosis for their kid's illness. Considerations concerning the timing of elective closure for clinically asymptomatic kids should take into account the high possibility of natural closure reliant upon earlier revealed prognosticators.

Declaration of interest

The authors report no conflicts of interest. The authors along are responsible for the content and writing of the paper.

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