LIBYAN JOURNAL OF MEDICINE
2022, VOL. 17, 2007603
https://doi.org/10.1080/19932820.2021.2007603

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Predictors of pulmonary hypertension among children with atrial septal defects (ASD)

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ABSTRACT

Introduction: Atrial septal defect (ASD) is a common congenital heart disease in children that uncommonly presents with pulmonary hypertension. Much is not known about the exact predictor of PAH in children with ASD.

Objectives: This study aimed to determine the predictors of pulmonary hypertension in children with ASD.

Patients and Methods: This was a descriptive analysis of children with ASD carried out in three different institutions over a five-year period. Data entry and analysis were done using IBM Statistical Package for Social Sciences (SPSS) statistical software, version 25.

Results: The majority of the participants, 52.2%, had pulmonary hypertension and 62.5% of them occurred as mild pulmonary hypertension. There was a very weak positive correlation between pulmonary hypertension and the size of atrial septal defect, increases in size of atrial septal defect correlate with increases in pulmonary hypertension and this was found not to be statistically significant ($n = 67$, $r = 0.193$, $p = 0.118$). There was a positive correlation between the size of atrial septal defect and the age of participants in months, increases in age correlate with increases in size of atrial septal defect and this was found to be statistically significant ($n = 67$, $r = 0.357$, $p = 0.003$).

The highest proportion of respondents who had pulmonary hypertension, 64.7%, was seen among children less than 1 year old while the least proportion, 27.3%, was within 1–5 years, and the difference in proportions was found to be statistically significant ($\chi^2 = 8.187$, $p = 0.017$).

Conclusion: Pulmonary hypertension in children with ASD occur usually in the mild form. Age is the only strong predictor of PAH in children with isolated ASD.

ARTICLE HISTORY
Received 13 August 2021
Accepted 13 November 2021

KEYWORDS
Atrial septal defect; pulmonary hypertension; children

1. Introduction

Atrial septal defect (ASD) is a common congenital heart disease in children, which occurs in 6–10% of all congenital heart diseases with overall prevalence estimated at 2 to 3.89 per 1000 children [1]. It is characterized by a left-to-right shunt, volume overload of the right heart and, with time, pulmonary over-circulation with attendant pulmonary arterial hypertension [2]. Pulmonary arterial hypertension usually occurs in children with ASD from progressive vascular remodeling from persistent left-to-right shunt and large size lesion enough to cause increased pulmonary blood flow [3–7].

About 9 to 35% of children with ASD present with pulmonary arterial hypertension (PAH) and this is seen more in children with the ostium secundum variety [8]. Similarly, echocardiographic assessment of children with ASD by Denise Van der Linde et al [8] showed that PAH was present in 45% of the patients, though his sample population were mainly among adult patients. Though a right heart catheterization is considered to be the gold standard for the diagnosis of pulmonary hypertension, however, the diagnosis of PAH and other cardiovascular diseases (CVDs) in sub-Saharan Africa is usually by echocardiography [9,10]. Echocardiography is performed in few referral centers due to low availability of facilities and human resources for cardiovascular care [10]. There is little or no data on predictors of pulmonary hypertension in children with ASD. Some studies have suggested age, size of the defect, and gender as possible predictors [11,12].

In this vicinity, no study had been carried out to ascertain the predictors of pulmonary hypertension in children with ASD. This study is thus aimed to ascertain the predictors of pulmonary hypertension in children with ASD, the prevalence of pulmonary hypertension and the impact of associated lesions on pulmonary hypertension.

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2. Methods

2.1. Study area and study design

This was a descriptive analysis of children with ASD carried out in three different institutions; namely, the University of Nigeria Teaching Hospital, Tender care hospital and Triple care hospital over a five-year period from 2016 to 2020.

2.2. Study population

Children with ASD who are aged one month to 18 years and attended the hospital under study were recruited consecutively.

2.3. Inclusion and exclusion criteria

Children with isolated ASD who were between the age of one month and 18 years and gave consent or assent were included in the study, while children with patent foramen ovale, children less than 1 month of age, and those with ASD dependent lesion like coarctation of the aorta, transposition of the great artery **and every other lesion that causes left to right shunt** were excluded from the study.

2.4. Consent

This was procured from the parents before embarking on echocardiography

2.5. Child assent

This was obtained in children who were older than seven years. The study had a quality control where other cardiologist made a diagnosis of congenital heart disease at different intervals so as to reduce bias.

2.6. Definition of ASD using echocardiography

Atrial septal defect is best visualized from the precordial, apical, and subxiphoid positions, with subxiphoid views showing the relationship between the atrial defect, AV valves, and interventricular septum. Atrial septal defect is seen as a deficient interatrial septum, and the size of the defect was measured in diastole [13,14].

2.7. Classification of size of ASD

Small defects occur with a maximal diameter > 3 mm to < 6 mm, moderate defects occur with a diameter of ≥ 6 mm to < 12 mm, and large defects occur when the diameter of ASD is ≥ 12 mm.

2.8. Assessment of pulmonary hypertension

Currently, the mean pulmonary arterial systolic pressure (mPAP) threshold for pulmonary hypertension is >20 mmHg [15,16]. Pulmonary hypertension was calculated in this study by adding the pressure gradient across the tricuspid valve and right atrial pressure.

The values of 8 mmHg were taken as right atrial pressure, and this was added to TR velocity. The value of 8 mmHg was taken as right atrial pressure since the IVC was neither collapsible nor dilated. According to the guidelines by Chemla et al [17], Pulmonary hypertension is defined as pulmonary artery systolic pressure of 30 mmHg [17]. Pulmonary hypertension was classified as mild = 30–50 mmHg; moderate = 51–65 mmHg and severe = > 65 mmHg [18].

2.9. Sample size estimation

Sample size in this study was determined using the formula.

$N = Z^2P\ (I - P)/\ D^2$

Z = 1.96, i.e. the level of significance

P = Prevalence of children with ASD (0.04) [1].

D = Tolerable error (0.05)

Using the above formula, the minimum sample size of 59 was obtained, 15% attrition rate was considered, and this brought the sample size to 67.

2.10. Data analysis

Data entry and analysis were done using IBM Statistical Package for Social Sciences (SPSS) statistical software, version 25. Continuous variables were defined using mean and standard deviation, while categorical variables were presented using frequencies and proportions. Correlation analysis, Chi square test, and odd ratio were used in the analysis. The level of statistical significance was determined by a p value of <0.05. In determining the predictors of pulmonary hypertension, variables with a p value of <0.2 on bivariate analysis were entered into the logistic regression model. The results were presented using adjusted odds ratio and 95% confidence interval, and the level of statistical significance was determined by a p value of <0.05.

3. Results

Table 1 shows the characteristics of the respondents. The median age of the respondents was 11.0 months. The majority of the respondents, 50.7%, were less than one year, while the least proportion, 16.4%, was more than 5 years. A higher proportion of the respondents, 52.2% were males.

Table 2 shows the prevalence of pulmonary hypertension. The majority of the participants, 52.2% had

pulmonary hypertension and 62.5% of them occurring as mild pulmonary hypertension. The highest proportion of the respondents, 40.3% had small atrial septal defects defect while the least proportion, 28.4% had large ASDs.

Table 3 shows correlation of pulmonary hypertension with size of atrial septal defect. There was a very weak positive correlation between pulmonary hypertension and size of atrial septal defect, increases in atrial septal defect correlates with increases in pulmonary hypertension and this was found not to be statistically significant (n = 67, r = 0.193, p = 0.118). There was a positive correlation between size of atrial septal defect and age of participants in months, increases in age correlates with increases in atrial septal defect and this was found to be statistically significant. (n = 67, r = 0.357, p = 0.003).

Table 4 shows association of pulmonary hypertension and characteristics of respondents. The highest proportion of respondents who had pulmonary hypertension, 64.7% were seen among children less than 1 year old while the least proportion, 27.3% were within 1–5 years and the difference in proportions was found to be statistically significant (χ^2 = 8.187, p = 0.017).

Table 5 shows association of atrial septal defect with characteristics of the respondents. The highest proportion of respondents who were less than one year had small ASD (60.4%) while the least proportion of those who had small ASD were among >5 years and the difference in proportions on the size of ASD of respondents was found to be statistically significant (χ^2 = 13.459, p = 0.009). Females are 1.5 times more likely to present with PAH compared to their male counterpart.

4. Discussion

This study is aimed at determining the predictors of pulmonary hypertension among children with isolated ASD. This study showed that 52.5% of children with isolated ASD had pulmonary hypertension; however, the majority of them presented with mild pulmonary hypertension. This simply suggest that pulmonary hypertension in children with ASD usually occurs in a mild form.

Other studies have noted lower prevalence of PAH as35% [13–21]. The low prevalence obtained in the above study could be explained by the fact that pulmonary hypertension was not graded into severity forms. Besides, another study has shown moderate to severe pulmonary hypertension (PAH) in ASD to have occurred in about 9–22% of their sample population while the mild variety occurred in about 78–91% [20,21].

This study showed a very weak positive correlation between pulmonary hypertension and size of atrial septal defect, and increases in atrial septal defect correlate with increases in pulmonary hypertension. That majority of our subjects presented with small size ASD could explain this weak correlation. Children with large size ASD also had higher degrees of left to right shunting, higher Qp:Qs ratios and

Table 1. Socio-demographic variables.

Variable	Frequency (n = 67)	Percent (%)
Age of respondents in months		
Minimum	1	
Maximum	204	
Median	11.0	
Mean±(SD)	36.1 ± 49.2	
Age of respondents		
<1 year	34	50.7
1–5 years	22	32.8
>5 years	11	16.4
Gender		
Male	35	52.2
Female	32	47.8

Table 2. Categories of ventricular septal defect and pulmonary hypertension.

Variable	Frequency (n = 67)	Percent (%)
Pulmonary hypertension		
Yes	35	52.2
No	32	47.8
Categories of pulmonary hypertension	(n = 35)	
Mild	22	62.9
Moderate	6	17.1
Severe	7	20.0
Categories of Arial septal defect		
Small	27	40.3
Moderate	21	31.3
Large	19	28.4

Table 3. Correlation of pulmonary hypertension with size of atrial septal defect.

Variable	Sample size (n)	Pearson correlation (r)	p value
Correlation of pulmonary hypertension with			
Size of atrial septal defect	(n = 67)	0.193	0.118
Age (months)	(n = 67)	−0.074	0.549
Correlation of size of atrial septal defect with			
Age (months)	(n = 67)	0.357	0.003

Table 4. Association of pulmonary hypertension and characteristics of respondents.

	Pulmonary hypertension (n = 67)		
Variable	Yes N (%)	No N (%)	χ^2 p value
Age of respondents			
<1 year	22 (64.7)	12 (35.3)	8.187 0.017
1–5 years	6 (27.3)	16 (72.7)	
>5 years	7 (63.6)	4 (36.4)	
Gender			
Male	19 (54.3)	16 (45.7)	0.123 0.726
Female	16 (50.0)	16 (50.0)	
Size of ASD			
Small	14 (51.9)	13 (48.1)	0.425 0.809
Moderate	10 (47.6)	11 (52.4)	
Large	11 (57.9)	8 (42.1)	

Table 5. Association of atrial septal defect and characteristics of respondents.

Variable	Size of ASD (n = 67) Small N (%)	Moderate N (%)	Large N (%)	χ^2 p value
Age of respondents				
<1 year	32 (60.4)	16 (30.2)	5 (9.4)	13.459 0.009
1–5 years	7 (26.9)	8 (30.8)	11 (42.3)	
>5 years	6 (46.2)	3 (23.1)	4 (30.8)	
Gender				
Male	18 (42,9)	15 (35.7)	9 (21.4)	1.650 0.438
Female	27 (54.0)	12 (24.0)	11 (22.0)	

greater propensity for developing pulmonary arterial hypertension [22–26]. It is revealing in this study that the highest proportion of children with ASD who had pulmonary hypertension were less than one year old. The work of Shilpa [27] et al has also shown that infant with ASD is more likely to develop PAH within the first 250 days of life. This could be explained by the fact that infants have reduced vascular growth, increased vascular tone and poor vasoreactivity. Additional pulmonary over circulation from anatomic shunts could further exacerbate pulmonary hypertension in these infants [27]. The influence of age on PAH on children with ASD has also been documented in other studies [28–30].

Though females present with higher propensity of having pulmonary hypertension in this study, but this was not significant. Several registries had shown that females are more susceptible to development of PAH. 'Estrogen paradox' or 'estrogen puzzle' of PAH, multiple elaboration of sex hormones, receptor mediated PAH and hormone signaling have all been implicated as the reason for the female preponderance [31–35].

5. Conclusion

Pulmonary hypertension in children with ASD occurs usually in the mild form. Age is the only strong predictor of PAH in children with isolated ASD.

5.1. Strength of the study

This is the maiden study in this vicinity, and literature in West Africa is rare. This article also draws strength from its multi-center nature. Besides, this study was done over a 5-year period.

5.2. Limitations

The sample size is relatively not large. However, ASD is not as common as VSD and PDAs in the general population.

Acknowledgments

We acknowledge Miss Carol who helped in data entry

Author contributions

JMC conceived and designed this study while JMC, ATC, COD and ENO helped in critical revision of the article. JMC and ENO also did the data analysis/interpretation. All authors have read and approved the manuscript.

Availability of data and materials

The datasets generated and analyzed during the current study are not publicly available so as to protect participants' anonymity, but are available from the corresponding author on reasonable request.

Disclosure statement

The authors declare that they have no competing interests.

Ethics approval and consent to participate

This complies with national guidelines. [23] All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standard. Ethical approval was obtained from the Ethics and Research committee of the University of Nigeria Teaching hospital Enugu (IRB number: 00002323).

Informed written consent was also granted by the parents/caregivers of subjects before they were recruited.

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