ORIGINAL ARTICLE

Pediatric Pulmonary Hypertension Secondary to Congenital Heart diseases in Nineveh province

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ABSTRACT

Background: Congenital heart diseases (CHD) and their associated pulmonary arterial hypertension (PAH) represent a real burden and challenge to the health services everywhere and needs extensive and continuous research.
Aims: To study the prevalence of PAH secondary to CHD as well as its characteristics and its associated risk factors.
Methods: This is across sectional study based on echocardiography (echo) conducted in the researchers' hospital over a 9 months period starting from 15th of May 2019. Data were collected using a specially designed questionnaire and analyzed using Microsoft excel 2013 and the statistical package for the social sciences (SPSS) 18 computer programs.
Results: The prevalence of PAH was (11.6 %) in the studied sample with mean age in months of 19.5 ± 3.37 standard error of mean (SEM) and 95% CI 12.9 to 26.1.The commonest causes of PAH secondary to CHD (PAH-CHD) were atrioventricular septal defect (AVSD), large or moderate size ventricular septal defects (L/MO VSD) and together contributed to more than half of the cases of PAH and they were (27.1%) and (25%) respectively. The frequency of developing PAH was also high in AVSD (81%) and L/MO VSD (75%) patients. There was significant positive correlation of mean pulmonary artery pressure (MPAP) with age ($P<0.05$ and $R^2 =0.26$). Parental low educational level, living in villages or being of Arab race all were significant risk factors for PAH.
Conclusion: There is high prevalence of PAH in association with CHD in Nineveh province pediatric population which is largely attributed to AVSD and L/MO VSD and positively correlated with age. The main risk factors to develop PAH were Arab race, low parental educational level, living in a village and Down syndrome. .
Keywords*:* Pediatric pulmonary hypertension, congenital heart diseases.

INTRODUCTION

Congenital heart diseases are ranking as one of the commonest congenital malformations affecting the fetus with a prevalence of up to 13/1000 live births and they have a significant impact on the child health, growth and development in addition to the burden reflected on both families and public health services[1,2].

In left to right shunt CHDs, the progressive increase in the pulmonary blood flow and hence its pressure may cause remodeling of the pulmonary vasculature (like thickening of medial muscle layer, thickening of intimal lining both eccentrically and concentrically and arterial obliteration) and eventually the development PAH or even shunt reversal i.e., Eisenmenger syndrome. The same pathophysiological changes can happen in some right to left shunt lesions if they are associated with unrestricted pulmonary blood flow like transposed great arteries with mixing defects in the absence of pulmonary stenosis. There are some data reporting a prevalence of PAH in 4-15 % of cases of CHD and up to 28 % in others[3,4,5]

Pulmonary hypertension secondary to CHDs (PAH-CHD), defined as mean pulmonary artery pressure(MPAP) ≥ 25 mmHg, is nowadays is less common than it was in the past decades because of the early diagnosis and better management of CHD. Down syndrome children represent a continuous challenge in this issue and contribute to as much as 18% of all cases of pediatric PAH-CHD and most of cases of PAH are attributed to AVSD among this population[6,7].

Echocardiography, although it isn't as accurate as invasive hemodynamic evaluation during cardiac catheterization, is the primary tool for the screening and evaluation of patients with PAH with high reliability. Tricuspid valve regurgitation and peak pulmonary valve regurgitation velocities by continuous Doppler are the main parameters utilized for estimating MPAP. Patients are classified according to the MPAP into mild (MPAP 25-40 mmHg), moderate (MPAP 41-55 mmHg) or severe (if the MPAP is > 55 mmHg) PAH[8-13].

The objective is to study the prevalence of PAH secondary to CHD as well as its characteristics and its associated risk factors.

PATIENTS AND METHODS

This is a case control cross sectional study conducted during the period from the 15th of May 2019 to 15th of February 2020 in the pediatric echocardiography and cardiology unit in the investigators hospital. Patients included were children aging <15 years with CHD and referred for echocardiographic evaluation due to variety of indications (e.g., heart murmur, follow up of already diagnosed CHD, cyanosis, palpitation, chest pain..etc) and their caregivers oral consent to participate in the study were taken. Involved patients evaluated echocariographically using Philips HDX7 system with 12 mHz and 2-4 mHz transducers. Patients were evaluated in the supine position using the standard echocardiographic views, tricuspid valve (TV) regurgitation and pulmonary

valve regurgitation velocities were measured in the apical 4 chamber and short axis parasternal views respectively to get the highest readings.

(Estimated Pulmonary Artery Systolic Pressure (EPASP) was calculated using the formula

EPASP= [(Peak TV regurgitation velocity)2 *4]+ right atrial pressure* .

***** Right atrial pressure is considered to be equal to 5-10 mmHg

MPAP was calculated as the following:

MPAP = 0.61 × ESPAP + 2 mmHgOr

MPAP=Peak pulmonary valve regurgitation pressure gradient)[11,14,15].

Any child identified with PAH was taken as index case and any next coming child with CHD for evaluation and if he/she didn't have PAH were taken as a control case for comparison and patients were labeled as PAH group or as NPAH group respectively. Patients with PAH were subdivided into 3 groups according to their MPAP, group A=Mild PAH, group B=Moderate PAH and group 3= Severe PAH. Different factors like patients' age, sex, residence, race, type of CHD, family history of CHD, person who is caring the child, use of PAH medications, and parental educational level were evaluated as possible risk factors to develop PAH in association with CHD. Patients were excluded from the study if they had any of the followings:

1. Parental refusal for participation in the study.
2. Children with any additional disease that may increase the PA pressure other than the CHD e.g., chronic respiratory diseases, sickle cell disease, connective tissue disease, primary pulmonary hypertension of the newborn,..etc.
3. Children with operated CHD, PDA in the first week of life or patent foramen ovale.
4. Children with poor echo window and or view due to variety of causes
5. Children with pulmonary venous hypertension due to left side obstructive diseases.

Statistical analysis was done using Microsoft excel 2013 and SPSS 18 software packages. P value was considered significant if it was < 0.05. Z test used for comparison of means and linear regression with Pearson coefficient were used to study correlations.

RESULTS

A total of 414 child < 15 years with both sexes (male/female =0.96) with different types of CHD were evaluated during the study period. Out of the studied sample48 child (11.6 %) with mean age in months of 19.5 ± 3.37 SEM and 95% CI 12.9 to 26.1, were identified with PAH. Among all causes of PAH, AVSD (27.1 %) and L/MO VSD (25 %) together contributed, nearly equally, to more than half of all cases of PAH (figure 1). Conversely speaking, as seen in figure 2, when all children with CHD (n=414) were considered, PAH showed the highest prevalence (100%) in TAPVR+ASD and followed again by ,L/MO PDA (87%) , AVSD (81%) and L/MO VSD (75%).

PAH did not show significant difference in the mean and median age when compared to the NPAH group at the time of evaluation (z calculated =0.478, not significant with $p<0.05$). Interestingly, with use of linear regression and Pearson correlation coefficient, there was a significantly positive correlation between patients' age and their MPAP within the PAH group, but it wasn't within the NPAH group ($p<0.05$, R^2 =0.3 versus p=0.3,R^2 =0.02) as seen in Fig.3.

The contribution of different cardiac malformations for the development of PAH had a statically significant difference for AVSD, large or moderate size VSD or PDA only), but the others were not (table 1).

Being villager, Arab race, illiterate or primary level of education of parents all were significant risk factors to develop PAH, also Down syndrome was significantly associated with PAH while being non syndromic was against the development of PAH as shown in table (2).

Within the PAH group, patients were subdivided into 3 sets (group A, B and C) as mild (MPAP 25-40 mmHg), moderate (MPAP=26-55 mmHg) and severe (MPAP> 55 mmHg) PAH. In group A the number was =17 (35.41%), group B it was =23 (47.91%) and group C it was =8 (16.66 %). When the over mentioned variables (used for comparison between PAH and NPAH) used again for comparison between the different groups of PAH and there was no significant difference in the frequency of different types CHD in relation to the severity of PAH. For the other comparable variables, the difference was significant if the patient is Down syndrome group B or being older than 12 months in group C while the intake of medications of PAH were significantly less frequent among group B.

Table 1: CHD causing PAH. Only AVSD, L/MO VSD and L/MO PDA have a statistically significant higher frequency among the PAH group. CHD (Congenital heart disease), PAH (pulmonary arterial hypertension), AVSD (atrioventricular septal defect), L/MO (large or moderate size), VSD (ventricular septal defect), PDA (persistent ductus arteriosus), ASD (atrial septal defect), DORV (double outlet right ventricle), TGA (transposed great arteries), PAPVR (partial anomalous pulmonary venous return), TAPVR (total anomalous pulmonary venous return).

CHD	PAH (n=48)	NPAH (n=48)	P
AVSD	13	3	S
L/MO VSD	12	4	S
L/MO PDA	7	1	S
L ASD	2	3	N
TAPVR+ASD	1	0	N
PAPVR+ASD	1	1	N
SINGLE VENTRICLE	2	2	N
DORV+ VSD	2	3	N
TGA+ASD/VSD	2	2	N
SMALL PDA+SMALL VSD	2	4	N
Others	4	25	N
Total	48	48	

Figure 1: CHD causing PAH. The main two causes were AVSD and L/MO VSD, together they contributed to more than half of cases.
CHD (Congenital heart disease), PAH (pulmonary arterial hypertension), AVSD (atrioventricular septal defect), L/MO (large or moderate size), VSD (ventricular septal defect), PDA (persistent ductus arteriosus), ASD (atrial septal defect), DORV (double outlet right ventricle), TGA (transposed great arteries), PAPVR (partial anomalous pulmonary venous return), TAPVR (total anomalous pulmonary venous return).

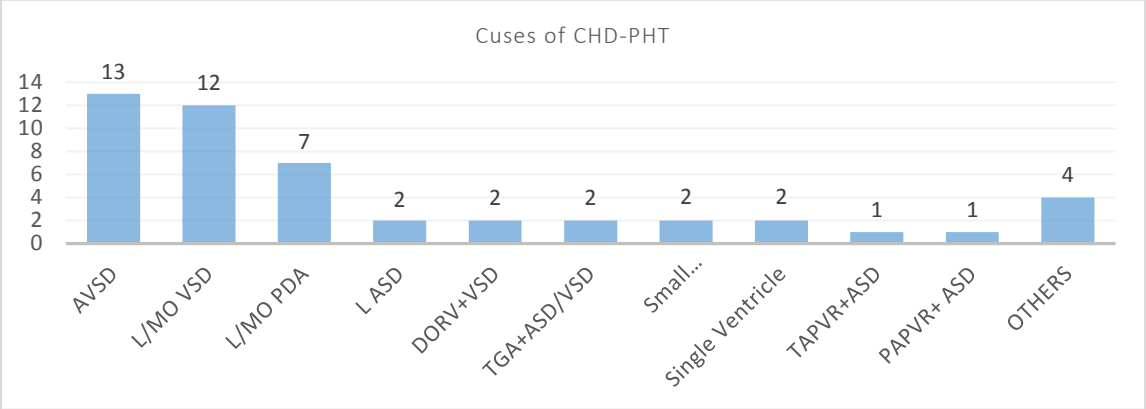

Figure (2: Frequency of development of PAH in different types of CHD.
CHD (Congenital heart disease), PAH (pulmonary arterial hypertension), AVSD (atrioventricular septal defect), L/MO (large or moderate size), VSD (ventricular septal defect), PDA (persistent ductus arteriosus), ASD (atrial septal defect), DORV (double outlet right ventricle), TGA (transposed great arteries), PAPVR (partial anomalous pulmonary venous return), TAPVR (total anomalous pulmonary venous return).

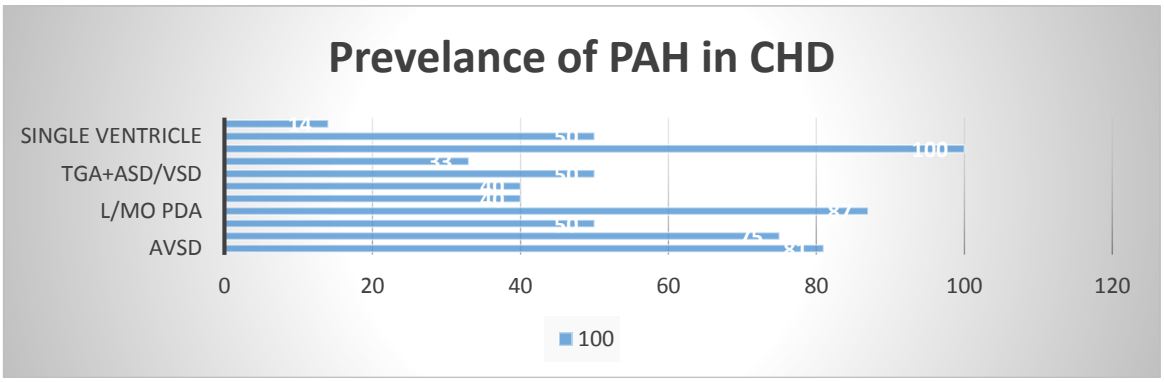

Figure 3: Correlation of MPAP with age among PAH group. There is significant positive correlation
PAH (Pulmonary arterial hypertension), MPAP (mean pulmonary artery pressure).

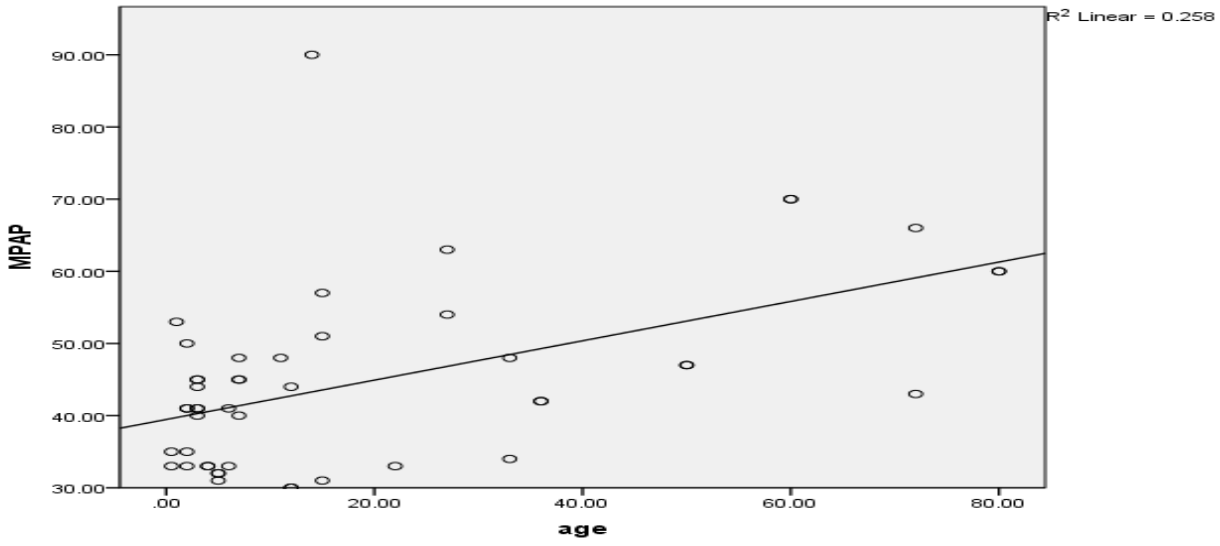

Table 2: Risk factors of PAH. Arab race, low educational level of parents, village residency and Down syndrome all are risk factors for PAH (pulmonary arterial hypertension).

Factors		PAH (%)	NPAH (%)	P
Gender	Male	23 (47.91)	22 (45.8)	N
	Female	25 (52.19)	26 (54.2)	N
Race	ARAB	40 (83.33)	31 (64.58)	S
	TURKMAN	3 (6.5)	5 (10.41)	N
	SHABAKI	4 (8.33)	7 (14.83)	N
	Others	1 (2.08)	5 (10.41)	N
Residence	City	31 (64.58)	37 (77.08)	N
	Town	5 (10.41)	7 (14.83)	N
	Village	12 (25)	4 (8.33)	S
Educational Level of parents	Illiterate	16 (33.33)	7 (14.83)	S
	Primary	11 (22.91)	3 (64.58)	S
	Secondary	11 (22.91)	19 (39.58)	N
	University	7 (14.83)	12 (25)	N
	Higher level	3 (64.58)	7 (14.83)	N
Caring Parent	Father	3 (64.58)	1 (2.08)	N
	Mother	6 (12.5)	5 (10.41)	N
	Both	35 (72.91)	39 (81.25)	N
	Others	4 (8.33)	3 (64.58)	N
Parental consanguinity	Positive	11 (22.91)	15 (31.25)	N
	Negative	37(77.08)	33 (68.75)	N
Syndromic	Down	26 (54.2)	5 (10.41)	S
	Edward	0 (0.0)	1 (2.08)	N
	Holt-Oram	1 (2.08)	0 (0.0)	N
	Pier robin	1(2.08)	1 (2.08)	N
	Non syndromic	20 (41.66)	41 (85.41)	S

Table 3: Risk factors of PAH among different groups of PAH patients. Down syndrome and lack PAH medications intake are significant risk factors for group B, while an age of ≥ 12 months is positively associated group C.

Factors		**Group A (n=17)**	**Group B (n=23)**	**Group C (n=8)**	**P**
Gender	Male	8	12	3	N
	Female	9	11	5	N
Race	ARAB	13	19	8	N
	TURKMAN	2	1	0	N
	SHABAKI	2	2	0	N
	Others	0	1	0	N
Residence	City	12	15	4	N
	Town	2	2	1	N
	Village	3	10	3	N
Educational Level of parents	Illiterate	2	12	2	N
	Primary	4	4	3	N
	Secondary	4	5	2	N
	University	4	2	1	N
	Higher level	3	0	0	N
Caring Parent	Father	2	1	0	N
	Mother	2	1	3	N
	Both	13	17	5	N
	Others	0	3	1	N
Parental consanguinity	Positive	3	7	1	N
	Negative	14	16	7	N
Syndromic	Down	2	12*	2	S
	Edward	4	4	3	N
	Holt-Oram	4	5	2	N
	Pier Robin	4	2	1	N
	Non syndromic	3	0	0	N
Patient age in months	Age ≥ 12 M	11	15	6*	S
	Age < 12 M	6	8	2	N
Intake of PAH medications	Yes	5	5	7	N
	No	12	18*	1	N

DISCUSSION

In many references CHDs are the commonest group of congenital malformations and accounts for up to 30% of the total (16). Among all CHDs related complications PAH represents a very important and serious entity, but in spite of that the weight of problem and its characteristics may be not adequately evaluated and possibly underestimated in our locality.

Epidemiologically speaking, the prevalence of PAH complicating CHDs is 5-10 %in the adolescent and adult populations in many studies, but the data about our country in general and in Ninevah province is very scanty especially in the pediatric population[17]. The prevalence of PAH (11.6%) in our studied sample of children was in the upper limit of the range that was found by other researchers[3-5] because many authors nowadays consider PAH-CHD complex primarily an adult problem more than being pediatric one due to the early diagnosis and management of CHD early in life before reaching the stage of PAH. This prevalence reflects inadequate estimation of the risk of the problem and probably insufficient evaluation of the risky children. According to Todd s Roth and Jamil A. Abulhosn (18), there is possible conversion to Eisenmenger syndrome in up to 50% of PAH-CHD if left untreated, making the prevalence in our studied sample a real challenge to health care services.

The study declared that AVSD followed by L/MO VSD accounted for (52%) of all causes of PAH-CHD, actually this is interesting observation in relation to AVSD being the first ranking CHD even before VSD, because it is well known that VSD is the commonest CHD. Understanding the pathogenesis of PAH-CHD explains our finding, PAH-CHD develops either because of large shunted volume under high pressure of shunt in the PA like in VSD or PDA , or with low pressure as in the case of ASD, and in the case of AVSD both volume and pressure of the shunt are higher compared to the others. The frequency of AVSD in our study was relatively high because of its association with Down syndrome (AVSD makes 45% of CHD in Down syndrome patients) which seems to be more common in our locality than in western countries which is explained by the legal and religious regulations that restrict abortions of abnormal fetuses and the lack of antenatal diagnosis of Down syndrome[19].

Although 50 % of VSDs may develop PAH according to N Fine et al[5], our study reported a relatively higher percentage (75%) of PAH in children with CHD because we did not involve small VSDs in this calculation which are not known to precipitate PAH and a higher figure (81%) in the cases of AVSD due to its pathological nature and high association with Down syndrome that by itself works as an additional risk factor for PAH.

The significant positive correlation of age with the MPAP among the PAH group seems to be logical and attributed to the length of time of exposure of the pulmonary circulation to the pathological effect of the shunt. Children of villagers or of those families with low educational level, in other words low socioeconomic level families according to Wali Omer and Tariq Al-Hadithiindex (20), were at a significant risk to develop CHD-PAH due to the inadequate family resources and knowledge to make a proper tracking of their children CHD. Arab race was additional risk factor to develop PAH-CHD and this is probably related to genetic factors that needs to be explained by further studies. Down syndrome is a risk factor to develop PAH-CHD which is a fact that has been proven by many studies[21-23] and our study supports this finding. Absence of father as a caring parent and lack of PAH medication were found to be more frequent in the moderate PAH (B) group which is likely to be related again to socioeconomic effects.

The lack of invasive evaluation of PA pressure by cardiac catheterization can be considered as some limitation to this study, however echocardiography results are highly reliable and the final outcome is not affected by this limitation.

CONCLUSION

There is high prevalence of PAH in association with CHD in Nineveh province pediatric population which is probably underestimated. AVSD and L/MO VSD are the main CHD contributing to PAH and needs careful follow up. PAH-CHD is positively correlated with age and as early as possible intervention is necessary to prevent it. The main risk factors to develop PAH were Arab race, low parental educational level, living in a village and Down syndrome and such risky patients need a special tracking.

Conflicts of interest :(The authors declare that there is no conflicts of interest regarding the publication of this manuscript or any financial support).

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