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Research Paper

Pulmonary Arterial Hypertension in Children with Congenital Heart Disease

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ABSTRACT:

BACKGROUND:

Pulmonary arterial hypertensions defined as the mean pulmonary arterial pressures more than 25mmHg at rest or more than 30mmHg with exercise no matter what age, or Tricuspid regurgitation with a Doppler velocity of more than 2.5 m/sec. In pediatric patients, it is defined as systolic pulmonary artery pressure exceeds 50% of systolic systemic pressure**.**

OBJECTIVE:

To describe the congenital cardiac defects that lead to pulmonary arterial hypertension in children, estimate the severity of pulmonary arterial hypertension associated with congenital heart disease, and to describe and evaluate the modality of diagnosis and treatment of pulmonary arterial hypertension in children with congenital heart disease.

PATIENTS AND METHOD:

Cross sectional study done in Iraqi center for cardiac disease in Gazi Al Hareri Hospital from 14th of December 2016 to 12th of July 2017. The study included 47 child their ages from (1-156 months)who approved to had Pulmonary arterial hypertension with congenital heart disease by echo study and or cardiac catheterization that done by pediatric cardiologist. Information were collected from their caregivers that included age,sex, time at diagnosis, family history ofcongenital heart disease , mode of diagnosis, type of treatment that child receive. Type ofcongenital heart disease and the severity of pulmonary arterial hypertension were approved by pediatric cardiologist.

RESULTS:

From a total number of 47 child that had congenital heart disease with Pulmonary arterial hypertension, 29 (61.7%) was males and 18(38.3%) was females. In this study, ventricular septal defect was found as the most common cause of pulmonary arterial hypertension. The mean age of the study group was 56months with range (1- 156) month. The mean age at diagnosis of congenital heart disease is 10month and the mean age of diagnosis of is Pulmonary arterial hypertension16month . Where 38 (80.9 %) patients were diagnosed with pulmonary arterial hypertension at early infancy , 2 (4.3 %) patients were diagnosed during late infancy and 7 (14.9 %) patients were diagnosed after infancy. There was statistically significant difference between the age of the patients and the severity of pulmonary arterial hypertension (P value 0.05) and there was statistical significance between the severity of Pulmonary arterial hypertension that associated with congenital heart disease and family history (P value 0.02).This study show there was no statistical significance between the severity of Pulmonary arterial hypertension and the type of congenital heart disease.

CONCLUSION:

The prevalence of severe pulmonary arterial hypertension in Iraq is high.

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INTRODUCTION:

than 30 mmHg with exercise, irrespective of other factors, or Tricuspid regurgitation with a Doppler velocity of over 2.5 m/sec. In pediatric patients, it is defined as systolic pulmonary artery pressure exceeding 50% of systolic systemic pressure.[1,2] While pulmonary arterial hypertension related to congenital heart disease (CHD) shares similar lung histology with idiopathic Pulmonary Arterial Hypertension,

there are notable differences between these causes.[3]

Pulmonary vascular disease in patients with congenital heart disease (CHD) is linked to higher mortality and morbidity rates. Despite increasing evidence supporting the benefits of PAH-specific therapies in the PAH-CHD population, the overall outcomes remain unsatisfactory.[4,5]

The estimated prevalence of congenital heart disease (CHD) is approximately 6-10 per 1,000 live births.[6,7] Among patients with CHD, the occurrence of pulmonary arterial hypertension (PAH) varies between 4-15%, depending on factors such as the size and location of the shunt. [8]

PAH was formerly categorized into two groups: primary pulmonary arterial hypertension (PPAH) or secondary pulmonary arterial hypertension, depending on the absence or presence of identifiable causes or risk factors. The diagnosis of PPAH involved a process of exclusion, ruling out all other potential causes of PAH. [9,10]

The most recent classification of pulmonary arterial hypertension (PAH) was established at the 4th World Symposium held in Dana Point.[11] However, this Dana Point classification does not fully capture the complexity of pediatric PAH, as it fails to encompass the diverse factors contributing to pediatric pulmonary hypertensive vascular disease.[12,13]

To address this limitation, current registries have started examining the etiology and outcomes of pediatric PAH. Among children, the majority of cases include idiopathic PAH, heritable PAH, and PAH associated with congenital heart disease (APAH- CHD), while cases of PAH linked to connective tissue disease are relatively rare.[14]

Infants with pulmonary arterial hypertension (PAH) often exhibit failure to thrive, tachypnea, and irritability due to low cardiac output. On the other hand, older children with PAH present symptoms similar to adults. Dyspnea on exertion is the most common initial symptom. Severe cases of PAH, particularly in IPAH and familial PAH patients, may be marked by near syncope or syncope.[15,16]

Over the past decade, the prognosis for children with PAH has improved significantly, thanks to the introduction of new therapeutic agents and more aggressive treatment approaches. However, due to the complex nature of the disease's origins and the limited data available for children with PAH, selecting appropriate treatment strategies remains challenging.[17,18]

Among all patients with congenital heart disease, those with Eisenmenger's syndrome experience the most significant functional impairment. The ability of Eisenmenger's syndrome patients to engage in day-to-day activities can be significantly impacted.(19,20)

AIM OF THE STUDY:

1. To describe the congenital cardiac defects that lead to PAH in children.
2. To estimate the severity of PAH associated with CHD.
3. To describe and evaluate the modality of diagnosis and treatment of PAH in children with CHD.

PATIENTS AND METHODS:

Settings and study design: A cross sectional study of children with CHD and PAH conducted in the cardiac consultation clinic in Iraqi center of cardiac disease in Ghazi Al- Hareri Hospital for 7 months duration from 14th December 2016 to 12th July 2017.

Ethical consideration: The study protocol is approved by Iraqi Board for Medical Specialties and Iraqi Center for heart diseases in Ghazi Al Hareri Hospital.

Definition of the case; inclusion and exclusion criteria: Only patients with CHD and PAH more than 25 mmHg are included in this study. Age from birth to 14 years old are included. Any patient with PAH that is not associated with CHD was excluded from this study.

Sampling: **patients visited the outpatient clinic on Wednesday of each week during the study period.**

Procedure of the study: 47 patients are encompassed in this study, every Wednesday from each week during the seventh months of data collection in the cardiac consultation clinic in Iraqi center of cardiac diseases in Ghazi Al Hareri Hospital, data was collected by the researcher. All patients with CHD and PAH in this study were diagnosed by echocardiogram and or cardiac catheterization. All patients' data were collected from the caregivers of the patients including age, sex, age at diagnosis, symptoms, admissions to hospital, family history of CHD, method of diagnosis and treatment. Type of CHD, severity of PAH were approved by the pediatric cardiologist at time of data collected and accordingly we subdivided the patients into two groups (patients with PAH ≤ 40mmHg and patients with PAH > 40 mmHg), this subdivision was done according to the start of treatment of the pulmonary arterial hypertension in the cardiac consultation clinic in Iraqi center for cardiac disease in Ghazi Al- Hareri Hospital.

Twelfth of patients were diagnosed at the time of data collection Most of patients were diagnosed by using echocardiogram which is the most commonly used imaging modality that was done by cardiologist using echocardiogram device (Vivid e9 U.S.E) equipped with s6 and m5sc probes. Others diagnosed by cardiac catheterization.

RESULTS:

A total of 47 patients with PAH that were associated with CHD were included in the study. The mean age at diagnosis of CHD is 10 months and the mean age of diagnosis of PAH is 16 ± 29 months.

Regarding the age at diagnosis of CHD, this study found 38 (80.8 %) of patients diagnosed during early infancy, 1 (2.1%) patient diagnosed during late infancy and 8 (17.02%) patients diagnosed after infancy. Where 38 (80.8%) patients were diagnosed with pulmonary hypertension at early infancy, 2 (4.3 %) patients were diagnosed during late infancy and 7 (14.9 %) patients were diagnosed after infancy. Twenty-nine (61.7 %) males and 18 (38.3 %) females. The mean age of the study group was 56±15 months with range (1 –156) month as shown in table 1.

Table 1: Distribution of cases of PAH according to their age at diagnosis.

Variable	No.	%
Age at diagnosis of PAH		
1− 6 months	38	80.8
7− 12 months	2	4.3
1-14 year	7	14.9
Gender		
Male	29	61.7
Female	18	38.3
Total	47	100

According to the type of CHD that cause the PAH , the patients were divided into two groups: patients that had cyanotic congenital heart disease 7 (14.9 %) and patients that had acyanotic heart disease 40 (85.1 %).The most common Congenital Heart Disease that caused Pulmonary Hypertension were: Ventricular Septal defect 10 (21.3 %), Atrial Septal defect 6 (12.8 %), Patent Ductus arteriosus 3 (6.4%), Ventricular Septal defect with Atrial Septal defect 10 (21.3%), Ventricular Septal defect with Patent Ductus arteriosus 6 (12.8 %), AV canal 5 (10.6 %), TGA 2 (4.3%), Epstein anomaly 1 (2.1 %), TAPVR 1 (2.1 %), Truncus arteriosus 3 (6.4 %), so the total number of patients that had VSD was 26 (55.4 %) and all patients with ASD was 16 (34.1%) (Table 2).

Table 2: Distribution of cases according to types of congenital heart disease with Pulmonary Hypertension.

Type of Heart defect	No.	%
VSD	10	21.3
ASD	6	12.8
PDA	3	6.4
VSD + ASD	10	21.3
VSD + PDA	6	12.8
AV CANAL	5	10.6
TGA	2	4.3
EPSTEIN ANOMALY	1	2.1
TAPVR	1	2.1
TRUNCUS ARTERIOSUS	3	6.4
Total		100

The percentage of syndromes associated with pulmonary hypertension were 7 (14.9%) patients with Down syndrome, 1 (2.1 %) patient with Cornelia de Lange syndrome. Twenty (42.6 %)

patients had recurrent admissions to hospital because of cyanotic attacks or shortness of breath, while 27 (57.4 %) patients had less than 3 admissions or no admissions at all.

Regarding the association between the presence of family history of congenital heart disease with or without pulmonary hypertension; 4 (8.5 %) patients were found to have positive family history while 43 (91.5 %) with negative family history, Table 3.

Table 3: Distribution of syndromes, recurrent admissions and family history in 47 cases with PAH.

Variable		No.	%
Non syndrome patients		39	83.0
Associated	Down Syndrome	7	14.9
syndrome	Cornelia de Lange	1	2.1
	Syndrome		
Recurrent	Yes	20	42.6
admissions	No	27	57.4
Family history	Positive	4	8.5
	Negative	43	91.5

As shown in Figure 1, the PAH was between 25-40 mmHg in 14.6% of patients, while more than 40 mmHg in 85.4% of them

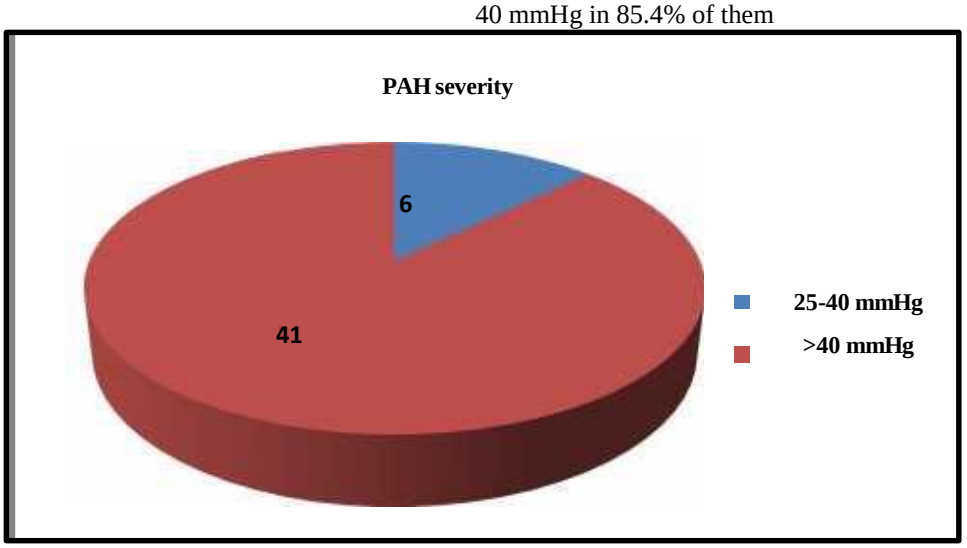

Figure 1: PAH severity in patients with CHD.

Regarding diagnosis of PAH of the patients, 41 (87.2 %) patients were diagnosed by echo study, 6 (12.8 %) patients were diagnosed by echo and catheterization. According to the type of treatment that patients received; patients were divided into four groups: patients with no treatment 12 (25.5 %), patients who received medical treatment 25 (53.2 %), patients undergone surgical repair 5 (10.6 %) and 5 (10.6 %) patients had cardiac catheterization to treat the cardiac cause of PAH. Table 4

Table 4: Distribution according to method of diagnosis and treatment of 47 cases with PAH.

variable		No.	%
	Echo study	41	87.2
Method of diagnosis	Echo and Cath	6	12.8
	No treatment	12	25.5
	Medical treatment	25	53.2
Type of treatment	Surgical treatment	5	10.6
	Catheterization	5	10.6

There was statistically significant difference between the age of the patients and the severity of pulmonary arterial hypertension in which 3 (60.0 %) of patients that there ages were less than one year had PAH more than 40mmHg while 38 (90.5%) of patients that there ages were more than one year found to have PAH more than 40 % (P value 0.05). Regarding the gender, this study shows no statistical significance between the sex and severity of pulmonary arterial hypertension P value (0.2) when 5 (17.2 %) of male children found to had PAH less than 40mmHg and 24 (82.8%) of them had PAH more than 40mmHg. About female patients, 1 (5.6%) of them with PAH less than 40mmHg and 17 (94.4%) with PAH more than 40mmHg. Table 5.

Table 5: Distribution according to the age and sex with severity of PAH of 47 cases with PAH.

Variable		PAH 25 – 40	%	PAH >40	%	P value
	0–1 year	2	40.0	3	60.0	**0.05**
Age	>1 year	4	9.5	38	95.5	
	Male	5	17.2	24	82.8	
Gender	Female	1	5.6	17	94.4	0.2

About the relation between the severity of PAH and the type of defect of CHD, this study shows there was no statistical significance. Regarding the presence of VSD, 3 (11.5%) patients had PAH less than 40mmHg and 23(88.5%) of them had PAH more than 40mmHg (**P value 0.7**). Patients with ASD, 1 (6.2%) of them had PAH less than 40mmHg while 15(93.8%) patients found to had PAH more than 40mmHg (P **value 0.3**). Patients that had PDA, 2(22.2%) of them had PAH less than 40mmHg and 7 (77.8%) with PAH more than 40mmHg (P **value 0.3**). Finally, patients with AV CANAL defect, 1(20.0%) of them had PAH less than 40mmHg while 4 (80.0%) found to had PAH more than 40mmHg (P **value 0.6**). Table 6.

Table 6: Distribution according the type of CHD and severity of PAH in 47 cases with PAH.

Variable		PAH 40mmHg	25-	%	PAH 40mmHg	> %	P value
VSD	Yes	3		11.5	23	88.5	0.7
	No	3		14.3	18	85.7	
ASD	Yes	1		6.2	15	93.8	0.3
	No	5		16.1	26	83.9	
PDA	Yes	2		22.2	7	77.8	0.3
	No	4		10.5	34	89.5	
AV canal	Yes	1		20.0	4	80.0	0.6
	No	5		11.9	37	88.1	
VSD & ASD	Yes	1		10.0	9	90.0	0.6
	No	5		13.5	32	86.5	
VSD & PDA	Yes	1		16.7	5	83.3	0.6
	No	5		13.2	33	86.8	

According to the type of CHD, this study showed no statistical significance between the type of CHD and severity of pulmonary hypertension. The patients were divided into two groups: Patients with cyanotic CHD and patients with a cyanotic CHD. Forty patients were found to have A cyanotic CHD, 5 (12.5%) of them had PAH less than 40mmHg and 35 (87.5%) had PAH more than 40mmHg. While 7 patients with cyanotic CHD, 1 (14.3%) of them had PAH less than 40 mmHg and 6 (85.7%) patients had PAH more than 40 mmHg (P value 0.8).

Seven patients with Down syndrome and 1 patient with Cornelia de Lange from the total number of the patients that included in this study found to have PAH more than 40 mmHg, while the patients with no syndromes 33(84.6%) of them have PAH more than 40mmHg and 6 (15.4%) with PAH less than 40 mmHg, that reveal there was no statistical significance between the severity of PAH and the presence of syndromic features (P value 0.4).Table 7

Pulmonary arterial hypertension (PAH) is characterized by mean pulmonary arterial pressures greater than 25 mmHg at rest or more

Table 7: Distribution according to the severity of PAH and the type of CHD , abnormal clinical features of 47 cases with PAH .

Variable		PAH 25-40 mmHg	%	PAH > 40 mmHg	%	P value
	Acyanotic	5	12.5	35	87.5	
Type of CHD	Cyanotic	1	14.3	6	85.7	0.8
	Normal	6	15.4	33	84.6	
Characteristic features	Features Down syndrome Cornelia de lange sybdrome	0 0	0 0	7 1	100.0 100.0	0.4

This study shows that there was statistical significance between the severity of PAH that associated with CHD and family history where 2 (50 %) of patients that had positive family history of CHD found to have PAH less than 40mmHg and 2 (50 %) of them with PAH more than 40. Four (9.3 %) of patients with negative family history of CHD in this study had PAH less than 40mmHg while 39 (90.7 %) of them had PAH more than 40 mmHg (P value 0.02). According to the history of recurrent admissions to hospital due to chest infection or respiratory distress and the severity of PAH, this study showed there was no statistical significance (P value 0.1) where 5 (18.5%) patients with negative history of recurrent admissions had PAH less than 40mmHg and 22 (81.5 %) of them with PAH more than 40mmHg. Those with positive history of recurrent admissions, 1(5.0 %) of them found to have PAH less than 40mmHg and 19 (95.0 %) with PAH more than 40mmHg. Table 8.

Table 8: Distribution of 47 cases with PAH according to the severity of PAH and family history and recurrent admissions.

Variable		PAH 25-40 mmHg	%	PAH> 40 mmHg	%	P value
Family history	+ ve	2	50.0	2	50.0	
	- ve	4	9.3	39	90.7	0.02
Recurrent admissions	+ ve	1	5.0	19	95.0	
	- ve	5	18.5	22	81.5	0.1

Regarding the relation between the method of diagnosis of PAH of patients that included in this study and the severity of PAH, no statistical significance was found (P value 0.1) where 4 (9.8 %) from patients that diagnosed with echocardiograph had PAH less than 40mmHg and 37 (90.2%) with more than 40mmHg. Two (33.3 %) patients with PAH less than 40mmHg were diagnosed by cardiac catheterization and 4 (66.7%) patients more than 40mmHg (P value 0.2). About the type of treatment of PAH and the severity of PAH, there was no statistical significance (p value 0.2). Where from patients who received no treatment, 1 (8.3%) patient had PAH less than 40 mmHg and 11 (91.7%) patients had PAH more than 40 mmHg, patients who received medical treatment 2 (8.0%) of them had PAH less than 40mmHg while 23 (92.0%) patients had PAH more than 40mmHg. About patients who underwent surgical correction of the cardiac defect, 1 (20.0%) patient had PAH less than 40mmHg and 4 (80.0%) of them had PAH more than 40mmHg. Patients who had cardiac catheterization for cardiac defect repair, 2 (40.0%) of them had PAH less than 40mmHg while 3 (60.0%) had PAH more than 40mmHg. Table 9.

Table 9: Distribution of 47 patients according to the severity of PAH and method of diagnosis and their treatment.

Variable		PAH 25-40 mmHg	%	PAH >40 mmHg	%	P value
	Echo	4	9.8	37	90.2	0.1
	Cath.	2	33.3	4	66.7	
	No treatment	1	8.3	11	91.7	
Treatment	Medical treatment	2	8.0	23	92.0	0.2
	Surgical treatment	1	20.0	4	80.0	
	Catheterization	**2**	**40.0**	**3**	**60.0**	

DISCUSSION:

The PAH accompanying CHD is a complicated disease presented by wide spectrum of morphological and haemodynamic pictures with different severity patterns. Understanding variables related to PAH severity is essential in planning for management of PAH-CHD.[21]

Present study found that prevalent age group of patients at diagnosis with was 1-6 months with predominance of male gender. These findings are inconsistent with results of Kücükoglu et al [22] Turkish nationwide registry which reported later age at diagnosis with predominance of female gender for patients with PAH and CHD. This inconsistency might be attributed to genetic variations between communities and clinical symptoms appearance. In our study, the ventricular septal defect was the common CHD among studied children. This finding is consistent with results of Al-Zuhairi study in Iraq.[23] Our study found that 14.9% of children with PAH-CHD were Down syndrome. This finding is close to results of Hopper et al [24] study in United States of America which reported that 11% of children with PAH-CHD were Down syndrome. In our study, 8.5% of children with PAH-CHD had positive family history of CHD. This finding is close to reports of Hansmann study [25] in Germany which stated that family history of CHD is positive among children with PAH-CHD.

This study found that 14.6% of children with CHD had PAH of 25-40 mmHg, while 85.4% of them had PAH of more than 40 mmHg. These findings are close to results of Landzberg et al [26] study in United States of America which documented higher prevalence of moderate PAH among children with CHD. However, our study prevalence of moderate to severe PAH was higher than results of AlSuwayfee et al [27] cross sectional study in Iraq which found that 58% of children with PAH-CHD had moderate to severe PAH. This difference may be due to discrepancy in sample size and methodology between different literatures. The current study showed that showed that 87.2% of children with PAH-CHD were diagnosed by echocardiography and 53.2% of them were medically treated. These findings are in agreement with reports of Zhao et al [28] study in China which documented that the majority of children with PAH-CHD were diagnosed by echocardiography and high proportion of them were managed medically.

In present study, increased age of children with CHD was significantly associated with increased severity of PAH (p=0.05). This finding coincides with results of Handoyo et al [29] study in Indonesia which found that younger age was a protective factor for uncorrectable congenital heart disease in children with pulmonary arterial hypertension. Our study found a significant association between negative family history of CHD and severe PAH (p=0.02). A study conducted in Spain by Cruz- Utrilla et al [30] revealed the importance of family history of CHD on development of PAH, but this effect may not affect the severity of PAH.

CONCLUSION:

The prevalence of severe pulmonary arterial hypertension in Iraq is high. Most of cases of pulmonary arterial hypertension that associated with congenital heart disease were found in male. The most common cardiac defect that causes pulmonary arterial hypertension was ventricular septal defect and most cases of patients with pulmonary arterial hypertension that associated with congenital heart disease were diagnosed in early infancy.

Conflicts of interest None **Acknowledgment**
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