Clinical and Parental Status of Patients with Congenital Heart Disease Associated Pulmonary Arterial Hypertension

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ABSTRACT: **Background:** Pulmonary arterial hypertension (PAH) is a significant consequence of congenital heart disease (CHD). Its presence and severity is associated with increased morbidity and mortality.

Objectives: To evaluate the clinical and demographic characteristics of adults with congenital heart diseases (ADCHD) and PAH at a single center.

Methods: A prospective registry of all patients with PAH was conducted between 2009 and 2015.

Results: Thirty-two patients were identified. The mean age at the last visit was 44 years (range 19–77 years). The prevalence of PAH among all ADCHD patients was 6% (95% confidence interval 4.3%–8.4%). A much higher prevalence (53%) was found in patients with Down syndrome. Most patients with PAH had moderate or severe disease. Fifteen patients (47%) were treated with pulmonary vasodilators and 6 (19%) with combination therapy. The average World Health Organization functional class was 2.6. Morbidity included cerebral vascular accident or transient ischemic attack in 22% (mostly in patients with right-to-left shunt) and arrhythmia in 37% of the patients. During a median follow-up of 3.5 years, 5 patients (15.6%) died. Of 13 women with no mental retardation, 11 were or had been married and all had children (between 1 and 13, mean 3.3).

Conclusions: Patients with congenital heart disease and PAH have significant morbidity and mortality. PAH is more prevalent in patients with Down syndrome. While pulmonary pressure during the reproductive years was not always known, 27% of women with PAH at the time of the study were multiparous.

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KEY WORDS: congenital heart disease, pulmonary arterial hypertension (PAH), adult mortality, Down syndrome, parity

Pulmonary arterial hypertension (PAH) associated with congenital heart disease is usually the result of a large systemic-to-pulmonary shunt. It often leads to right ventricular failure and early death [1]. The prevalence of this phenomenon differs in various reports. The Euro Heart Survey on adult congenital heart disease (CHD), which is a retrospective cohort study with a 5 year follow-up, reported PAH in 28% of patients [2], while a Dutch registry showed a PAH prevalence of only 4.2% [3]. The presence of a septal defect with right-to-left shunt, defines the Eisenmenger syndrome. During the past 50 years, the prevalence of Eisenmenger syndrome in the Western world has declined by an estimated 50% [5]. In a Dutch registry of adults with congenital heart disease, Eisenmenger syndrome was present in 6.1% of patients with septal defects [3]. The most common underlying anomalies were unrepaired complete atrioventricular canal and ventricular septal defect. A significant portion of the patients with PAH (30–45%) had Down syndrome [5].

Eisenmenger syndrome differs significantly from other types of pulmonary hypertension with respect to the cardiac anatomy, physiology, and natural history [6]. However, current understanding suggests that the pulmonary vascular changes are similar [7]. It has a somewhat better prognosis compared to other types of pulmonary arterial hypertension [8]. Patients with Eisenmenger syndrome have very limited exercise capacity [9]. In women with pulmonary hypertension and Eisenmenger syndrome, pregnancy carries a high risk with a high maternal and fetal mortality rate [10]. New therapy for pulmonary hypertension has been shown to improve hemodynamics, functional capacity [6,11,12], and survival [13] in patients with Eisenmenger syndrome.

The Israeli population is a diverse one, consisting of many immigrants from countries with suboptimal pediatric cardiology care. In some communities, women are expected and encouraged to bear many children. The prevalence, clinical characteristics, and parity of our cohort may thus be different from published data.

The aim of this study was to evaluate the clinical and demographic characteristics of adults with congenital heart diseases and pulmonary arterial hypertension in a single center in Jerusalem, Israel.

PATIENTS AND METHODS

The study was approved by the institutional ethics committee. A cross-sectional study to identify all patients with congenital heart disease was conducted at Hadassah Medical Center.

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Patients with patent foramen ovale were excluded. Pulmonary arterial hypertension was defined as a systolic pulmonary arterial pressure greater than 40 mmHg, estimated by echocardiography (tricuspid regurgitation gradient greater than 35 mmHg), or mean pulmonary artery pressure greater than 25 mmHg and pulmonary vascular resistance (PVR) greater than 3 Um^2 by right heart catheterization. Patients with elevated left atrial pressure (left ventricular end diastolic pressure greater than 15 mmHg) at catheterization or signs of diastolic dysfunction by echocardiogram were excluded. Demographics, medical history, echocardiography results, catheterization, laboratory, and functional data were collected. Mental retardation was defined as the mental inability to carry out normal independent living. The duration of the PAH was estimated by the first time PAH was diagnosed, or from birth in uncorrected post tricuspid non-restrictive lesions.

STATISTICAL METHODS

The Student's *t*-test was used for comparison of continuous variables that were normally distributed. Chi-square test was used to compare proportions. Confidence interval was calculated by Wald method. $P < 0.05$ was regarded as significant.

RESULTS

Between 2009 and 2015, 527 adults with congenital heart disease were seen at the Adult Congenital Heart Disease Unit at Hadassah Medical Center [Figure 1]. Of these, 297 (56%) were female, the mean age at the last visit was 32 years (range 17–83 years). Fifty-one patients (9.6%) were found to have mental retardation. Of these, 15 patients (3% of the total adults with congenital heart diseases [ADCHD]) had Down syndrome. The mean age of Down syndrome patients at the first follow-up was 26.2 years (median 31.5 years) and at the last follow-up, 32 years (median 38 years). Of the whole cohort of ADCHD patients, 244 patients had septal defects other than patent foramen ovale, 100 had atrial septal defects, 81 patients had ventricular septal defects, 36 patients had patent ductus arteriosus (PDA), 10 patients had atrioventricular canal, 6 had partially anomalous pulmonary venous drainage, 2 had aortopulmonary window (a congenital defect between the ascending aorta and the pulmonary artery), and 9 had other complex lesions (some patients had more than one diagnosis).

Of the 527 ADCHD patients, 32 (6%, 95% confidence interval 4.3–8.4) were found to have pulmonary hypertension not related to impaired left ventricular function. Eighteen (56%) were female. About one-third of the patients, both Down and non-Down syndrome had previously undergone repair of the defect. The median follow-up was 3.5 years, range 0.3–6.5 years. The mean age at the last visit was 44 years, range 19–77 years, median 41 years. The prevalence of PAH was 13% of patients with septal defects. Of the 32 patients with PAH, 10 (31%) had Eisenmenger syndrome. Eisenmenger syndrome prevalence was 4.1 % of the patients with septal defects. Table 1 compares patients with and without PAH.

CONGENITAL HEART DISEASE OF PATIENTS WITH PAH

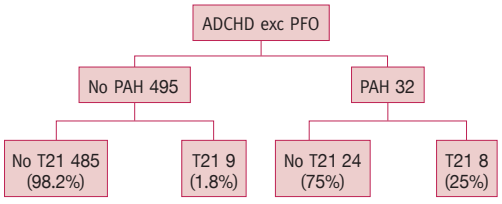
The cardiac diagnosis of the patients was:

- 10 ventricular septal defects
- 6 ductus arteriosus or AP window
- 8 atrial septal defects
- 3 atrioventricular canal
- 5 complex congenital heart disease

DOWN SYNDROME

Of the 32 patients with PAH, 10 patients (31%) had mental retardation. Of these, 8/10 had Down syndrome. The prevalence of PAH in patients with Down syndrome was 53% (8/15), compared to 4.7% in patients without Down syndrome (24/512 ADCHD patients excluding Down syndrome, $P < 0.001$). The prevalence of PAH in non-Down syndrome patients with mental retardation was (5.5%), not different from the prevalence of PAH in the rest of the patients. Table 2 compares the Down syndrome patients with the non-Down syndrome patients. In our series of patients with PAH, Down syndrome patients

Figure 1. Pulmonary arterial hypertension in adults with congenital heart disease



ADCHD = adults with congenital heart diseases, PFO = patent foramen ovale, PAH = pulmonary arterial hypertension

Table 1. Comparison of patient with and without PAH

N	No PAH 495	PAH 32	*P*
Age (median)*	27.8 ± 11.6 (23)	42.6 ± 20.1 (38)	‹ 0.001
Male (%)	218 (44)	14 (44)	NS
Down syndrome (%)	7 (1.4)	8 (31)	‹ 0.05
Post surgery (%)	233 (47)	15 (47)	NS
Number of surgeries (mean)**	1–5 (1.5)	1–5 (1.6)	NS
Arrhythmia (%)	71 (14)	11 (34)	0.0024
Death (%)	1 (0.2)	5 (15)	‹ 0.05

*Age at first visit. Comparison of age was significant when equal variance assumed or not assumed.

**Number of surgeries includes only those patients who had surgery

NS = non-significant, PAH = pulmonary arterial hypertension

were younger (age at first visit was 28 ± 9 years vs. 45 ± 20 years for non-Down, $P = 0.03$). None of the Down syndrome patients had arrhythmia, whereas 46% of those without Down syndrome suffered from arrhythmia. The pulmonary pressure was not different in the two groups.

Pulmonary pressure was measured by hemodynamic catheterization in 16 patients (50%) and estimated by echocardiography in 16 patients. Systolic pulmonary artery pressure measured by catheterization was 37–150 mmHg, average 82 mmHg. Seven patients (22%) had mild PAH (systolic PAP < 50 mmHg), 12 patients (37%) had moderate PAH (systolic PAP 50–70 mmHg), 13 patients (41%) had severe PAH (systolic PAP > 70 mmHg). The World Health Organization (WHO) functional class ranged from 1 to 4, with an average of 2.6. For the whole group, O_2 saturation at rest ranged from 77% to 99%, average 90%. Thirteen patients (41%) had O_2 saturation below 92%.

Thirteen patients (41%) had one to four surgical procedures, 15 (47%) had no intervention. Three patients had catheterization closure of atrial septal defect and one patent was diagnosed with ductus arteriosus in adulthood, with subsequent improvement of the pulmonary pressure in all.

The duration of PAH (from diagnosis or from birth in uncorrected lesions with PAH from birth) ranged from 4 month to 57 years, average 15.8 years, median 13 years. During a median follow-up of 3.5 years, five patients (15.6%) died. The age at death ranged from 29 years to 73 years, mean 51 years.

Five patients suffered CVA, and two others had TIAs. Arrhythmia occurred in 46% of the non-Down syndrome patients. No Down syndrome patient had arrhythmia. Eleven patients had other non-congenital heart diseases, such as thalasemia, ischemic heart disease, pulmonary embolism, hypothyroidism, or diabetes.

MARITAL STATUS AND PARITY

Of the patients with pulmonary hypertension, 10 patients were mentally impaired. Of the 22 patients who were not mentally impaired, 15 (68%) were married, one was a widow, one divorced, and 5 were single. Of the 17 patients who were married or had been married (widow or divorced), 15 had 1 to 13 children. There were 13 women with no mental retardation. Of these, 9 were married, one divorced, one a widow, two had never married. Eleven women (85% of women with normal intelligence) were or had been married. Of these women, all had children (1 to 13, average 3.3 children per woman). As shown in Table 3, three women (27% of women with children) had 4, 8, or 13 children.

Pulmonary hypertension severity of the women with children at the time of assessment was severe in four, moderate in six, and mild in one. Pulmonary hypertension severity of the seven women without children at the time of assessment

Table 2. Comparison of PAH patients, Down syndrome and non-Down syndrome

	Down n (%)	Non Down n (%)	p (Down vs. non Down)
Number	8	24	
Male	3 (37)	11 (46)	NS
Age* mean (range)	29 (19–42) Med 38	49 (21–77) Med 41	0.03
Cardiac lesion AV canal PDA VSD ASD only Complex	 2 (25) 5 (62) 2 (25) 0 0	 1 (4) 1 (4) 8 (33) 8 (33) 6 (25)	 0.08 0.001 NS 0.06 NS
Post-repair	3 (37)	6 (28)	NS
Sat < 92%	3 (37)	11 (46)	NS
Sat mean (range)	90 (80–96)	91 (77–99)	NS
PAP last cath	59 (n=3)	87 (n=13)	NS
PAP mean	46	51.6	NS
PAH medications	2 (25)	7 (29)	NS
NYHA mean	2.6	2.6	
Arrhythmia	0	11 (46)	0.018
CVA/TIA	1 (12)	6 (25)	NS

AV canal = atrioventricular canal, PDA = patent ductus arteriosus, VSD = ventricular septal defect, ASD = atrial septal defact, NYHA = New York Heart Association functional class, CVA/TIA = cerebrovascular accident/ transient ischemic attack, PAH = pulmonary arterial hypertension, PAP = pulmonary artery pressure

Table 3. Characteristics of women with children (n=11)

Number of children	Last visit age	CHD	PAH medications	NYHA	PAH severity	PAP	Cath mean PAP
4	Died at 61	S/P ASD & TAPVD	Refused cath	2.0	Moderate	60 (echo)	
2	32	DORV	Sildenafil	3.0	Moderate	70 (echo)	
1	22	S/P VSD	Bosentan changed to sildenafil	1.0	Severe	65	46
1	74	ASD		3.0	Moderate	65	30
2	Died at 50	LTGA PS	Bosentan sildenafil, treprostinil	4.0	Severe	150	80
8	53	PDA			Moderate	47	27
1	22	S/P VSD and coarctation	Sildenafil mecitentan	1.0	Severe	92	56
2	67	S/P SV ASD PAPVD		2.0	Mild	60 (echo)	
2	71	Palliated ToF	Sildenafil	3.0	Mod	60	44
1	77	ASD	Ambrisentan, sildenafil, iloprost inh.	3.0	Severe	130	68
13	61	ASD bicuspid aortic valve		3.0	moderate (borderline post closure)	81	45

ASD = atrial septal defect, AV canal = atrioventricular canal, cath = catheterization, CHD = congenital heart disease, DORV = double outlet right ventricle, LTGA = corrected transposition of the great arteries, NYHA = New York Heart Association functional class, PAH = pulmonary arterial hypertension, PAP = pulmonary artery pressure, PAPVD = partially anomalous pulmonary venous drainage, PDA = patent ductus arteriosus, PS = pulmonary valve stenosis, SV = sinus venosus, ToF = Tetralogy of Fallot, TAPVD = totally anomalous pulmonary venous drainage, VSD = ventricular septal defect

was severe in three, moderate in three, and mild in one. The woman with 13 children was diagnosed with a large atrial septal defect at the age of 61. At catheterization she was found to have systolic pulmonary pressure of 81 mm/Hg, mean 45 mmHg, a wedge pressure 8 mmHg. The Qp/Qs was 2.5:1 and pulmonary vascular resistance was 6.1 Um2. She reportedly had had 13 uneventful pregnancies and deliveries, and three miscarriages. She underwent catheterization to close the atrial septal defect (ASD) with decrease in tricuspid regurgitation (TR) gradient from 60 mmHg to 30 mmHg.

The woman with eight children had a moderate size PDA diagnosed at 53 years of age. She had moderate pulmonary hypertension as assessed by echo with TR gradient of 60 mmHg, but only mild pulmonary hypertension at catheterization; systolic pulmonary pressure 47 mmHg, mean 27 mmHg. She underwent closure of the PDA; tricuspid regurgitation gradient decreased from 60 mmHg to 27 mmHg after the closure. Another case was a 21 year old woman with previous repair of coarctation of the aorta and ventricular septal defect (VSD) closure who presented at the 8th week of gestation. Catheterization showed pulmonary hypertension (PAP 90/60 mmHg). She was not willing to terminate the pregnancy and was treated with sildenafil during pregnancy and had an elective caesarian section at 34 weeks. Toward the end of gestation and following delivery, the severity of the tricuspid regurgitation worsened and pulmonary pressure increased. Sildenafil dose was increased and bosentan was added after delivery.

MEDICATIONS

Fifteen patients (47%) were treated with pulmonary vasodilators. Ten patients were treated with endothelin receptor antagonists, ten were treated with sildenafil, and seven patients (all with severe PAH) were treated with combination therapy. Twenty-two patients were treated with other non-PAH medications.

LABORATORY DATA

Blood count was available in 27 patients, Hemoglobin: range 11–20 gr%, mean 14.3 gr%. Mean corpuscular volume (MCV) was in the normal range in all patients. Creatinine was normal in all but one patient on dialysis.

DISCUSSION

PAH is a relatively rare disease. Multicenter studies may provide larger study populations. However, single-center reports are important and provide additional information that may be incorporated into meta-analysis and contribute to our understanding of this disease. In addition, detailed reports of patient characteristics may provide information lacking from large studies.

The prevalence of ADCHD patients with PAH in this cohort was 6%, and 4.1% of patients with septal defects, similar to that reported in the Dutch registry figure [3] and lower than the reported figures in the Euro Heart Survey [2]. A much higher prevalence of PAH (53%) was found in Down syndrome patients, as reported by Diller and co-authors [5]. Non-Down syndrome patients with mental retardation were not at higher risk for PAH. Most patients with PAH had moderate or severe disease. The duration of PAH reported here is, of course, an underestimation, as many patients were found to have PAH late in life, probably after many years of undiagnosed disease. Nearly half of the patients were treated with targeted PAH medications. As the indication for therapy in Israel requires reduced functional capacity, not all patients met the criteria for treatment. Morbidity in this patient group was significant and included CVA or TIA in 22% and arrhythmia in 34%. The age of patients with PAH was significantly older than that of patients without PAH. This observation could have contributed somewhat to the higher degree of arrhythmia, but not mortality, which was insignificant in the non-PAH group.The majority of women in our cohort who were not mentally disabled were, or had been, married and had children, with a few having a large number of children. As many of the women were diagnosed at a late age, it is hard to know what the pulmonary pressure was at the time they were having children. One can speculate that these women had some degree of pulmonary hypertension during their reproductive years. It is not uncommon in our practice to care for women with moderate to severe pulmonary hypertension who chose to become pregnant and give birth despite being warned about the risk by the medical staff. This phenomenon is a result of a cultural norm in some communities in Israel, and especially in Jerusalem, that encourages women to have many children. Some women, even though they realise that pregnancy and delivery may endanger their life, still choose to become pregnant as being childless seems to be a worse choice for them and their families.

The mortality of our cohort was 15.6% during a median follow-up of 3.5 years. This is not very different from published figures. In the REVEAL trial, Barst et al. [14] reported 22% mortality at the 4 year follow-up and 30% at 7 year follow-up in patients with congenital heart disease related PAH. The mean age of our patients was similar to that of the REVEAL patients (in the present study 44 years, in the REVEAL 37–41 years). In another study, Schuuring et al. [15] reported a median follow-up of 4.7 years in 91 patients of similar age. The 1 and 8 year mortality rates were 7.3% and 37.3%, respectively.

LIMITATIONS

The single-center study comprised a small number of patients and relatively short follow-up time. As in other similar studies, the diagnosis of pulmonary hypertension was not confirmed by catheterization for all patients. Mental retardation was defined by the ability of independent living and not by intelligence tests, thus milder forms of mental impairment may have been missed.

CONCLUSIONS

Adult patients with congenital heart disease and PAH have significant morbidity and mortality rates. Down syndrome patients are at a higher risk for PAH, but mental retardation alone is not a risk factor for PAH. While pulmonary pressure during the reproductive years was not always known, 27% of women with PAH at the time of the study were multiparous.

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Capsule

Application of real-time global media monitoring and 'derived questions' for enhancing communication by regulatory bodies: the case of human papillomavirus vaccines

The benefit-risk balance of vaccines is regularly debated by the public, but the utility of media monitoring for regulatory bodies is unclear. A media monitoring study was conducted at the European Medicines Agency (EMA) concerning human papillomavirus (HPV) vaccines during a European Union (EU) referral procedure assessing the potential causality of complex regional pain syndrome (CRPS) and postural orthostatic tachycardia syndrome (POTS) reported to the authorities as suspected adverse reactions. To evaluate the utility of media monitoring in real life, prospective real-time monitoring of worldwide online news was conducted from September to December 2015 with inductive content analysis, generating 'derived questions'. The evaluation was performed through the validation of the predictive capacity of these questions against journalists' queries, review of the EMA's public statement and feedback from EU regulators. A total of 4230 news items were identified containing personal stories and scientific and policy/process-related topics. Explicit and implicit concerns were identified, including those raised due to lack of knowledge or anticipated once more information would be published. Fifty derived questions were generated and categorized into 12 themes. The evaluation demonstrated that providing the media monitoring findings to assessors and communicators resulted in (1) confirming that public concerns regarding CRPS and POTS would be covered by the assessment; (2) meeting specific information needs proactively in the public statement; (3) predicting all queries from journalists; and (4) altering the tone of the public statement with respectful acknowledgement of the health status of patients with CRSP or POTS. The study demonstrated the potential utility of media monitoring for regulatory bodies to support communication pro-activity and preparedness, which is intended to support trusted safe and effective vaccine use. Derived questions seem to be a familiar and effective format for presenting media monitoring results in the scientific-regulatory environment. It is suggested that media monitoring could form part of regular surveillance for medicines of high public interest. Future work is recommended to develop efficient monitoring strategies for that purpose.

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