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The Swiss registry for pulmonary arterial hypertension: the paediatric experience

For the Swiss Society for Pulmonary Hypertension

Margrit Suzanne Fasnacht[a], *Jean-François Tolsa*[b], *Maurice Beghetti*[c]

[a] University Children's Hospital Zurich,
[b] University Children's Hospital Lausanne,
[c] University Children's Hospital Geneva

Summary

Background: Pulmonary arterial hypertension is a rare disease with a poor prognosis. Epidemiological data are scarce, particularly in the paediatric population. A registry was recently developed in order to collect epidemiological data on patients with pulmonary arterial hypertension (PAH) in Switzerland. This is the first description of the paediatric data.

Methods: Paediatric patients aged 0–18 years with the diagnosis of PAH were enrolled in the registry from 1999 to 2005 with informed consent from their parents. Patient characteristics, PAH aetiology, functional capacity, exercise capacity, treatments and outcome were among the most important data collected.

Results: A total of 23 patients (12 male, 11 female) have been thus far included in the registry. Median age at time of diagnosis was 3 years (range 1 month–18 years) and median follow-up was 3.47 years (range 1 day–12.6 years). PAH aetiologies are diagnosed as idiopathic in 8/23 patients (34.8%) and associated with congenital heart diseases in 12/23 (52.2%) or with pulmonary diseases in 3/23 patients (13.0%). Death occurred in 1 patient before treatment was initiated. Single treatments include medications with a calcium channel blocker in 2/23 patients, with bosentan in 10/23, and with inhaled iloprost in 1/23. Combined therapies include bosentan and inhaled iloprost in 7/23 patients, bosentan and sildenafil in 2/23 patients, and bosentan, sildenafil and inhaled iloprost in 2/23 patients. Additional oral anticoagulation is given to 14/23 patients and 8/23 patients are on oxygen therapy. NYHA class at baseline visit was obtained in 22/23 patients (4 NYHA 2, 17 NYHA 3 and 1 NYHA 4). Changes in NYHA class were observed over a 2-year period in 3/22 patients who improved from NYHA 3 to NYHA 2. Initial improvement of 6-minute walk distance was observed in 6/13 patients with a sustained improvement in 4.

Conclusion: These preliminary results provide information on the epidemiology of PAH in children in Switzerland and demonstrate that most paediatric patients show stabilisation of the disease under new treatments. This underscores the utility of registries for rare diseases in providing crucial information in the era of new therapies. It may also help to improve the future medical approach.

Key words: registry; pulmonary arterial hypertension; children

Introduction

Pulmonary arterial hypertension is a rare disease in childhood associated with a poor prognosis if left untreated [1, 2]. The most common causes of PAH in the paediatric population are idiopathic or familial forms, congenital heart disease with left-to-right shunt, and neonatal lung diseases. Persistent pulmonary hypertension of the newborn is a particular form of pulmonary arterial hypertension which will be recorded separately. Before the era of new treatments for PAH, the reported median survival for children was 10 months after diagnosis [3]. Outcome seemed to be worse in children than in adults.

During the last two decades tremendous advances in understanding of the pathogenesis of pulmonary vascular disease have been made. These have led to the introduction of new therapies which have greatly improved patient prognosis and survival.

However, epidemiological data are still scarce, especially in the paediatric population. Since 1999 a Swiss registry for patients with pul-

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monary arterial hypertension has been launched under the guidance of the Swiss Society for Pulmonary Hypertension [4]. Included in the registry are all forms of PAH except the persistent pulmonary hypertension of the newborn. In agreement with the Swiss Society for Pulmonary Hypertension some data were entered retrospectively. Cooperation between all the specialised centres in Switzerland has made it possible to include all paediatric patients presenting with PAH in this registry and collect epidemiologic data.

Methods

Paediatric patients from age 0–18 years with the diagnosis of pulmonary arterial hypertension of all aetiologies except persistent pulmonary hypertension of the newborn were enrolled in the registry from 1999–2005 with informed consent from the parents. The registry is a national multicentre, observational non-interventional programme. The patients were enrolled after diagnosis or when therapy was initiated or intended. Thus some patients have baseline visits long before enrolment in the registry and were entered retrospectively (in agreement with the Swiss Society for Pulmonary Hypertension). The data collected in the registry include patient characteristics, pulmonary arterial hypertension aetiology, patient's vital signs, right heart catheter data, echocardiographic data, functional capacity, exercise capacity, treatments and outcome. The data presented are a description of the data collected in the registry. Because of the small patient numbers and the heterogeneity of the patients, no statistical analyses were performed.

Table 1

Patient	CHD, other diagnosis	Operation	Age at operation	PAH at time of operation
1	d-TGA, VSD	Balloonatrioseptostomy, Pulmonary artery banding, Arterial switch, Debanding, VSD closure	1day 1 week 4 months	No
2	d-TGA	Palliative Senning, partial VSD closure	15 months	Yes
3	AP window	AP window closure	7 years	Yes
4	AVSD Down syndrome	No		
5	VSD, Down syndrome	VSD closure	7 months	Yes
6	VSD, Down syndrome	No		
7	VSD	No		
8	VSD	Yes	3 years	No
9	VSD	No		
10	VSD	Yes	10 years	Yes
11	ASD sinus venosus type	No		
12	PDA	No		

Abbreviations: CHD = congenital heart disease, PAH = pulmonary arterial hypertension, d-TGA = Transposition of the great arteries, VSD = ventricular septal defect, Senning operation = atrial switch operation, AP window = aortopulmonary window, AVSD = atrioventricular septal defect, ASD = atrial septal defect, PDA = patent ductus arteriosus.

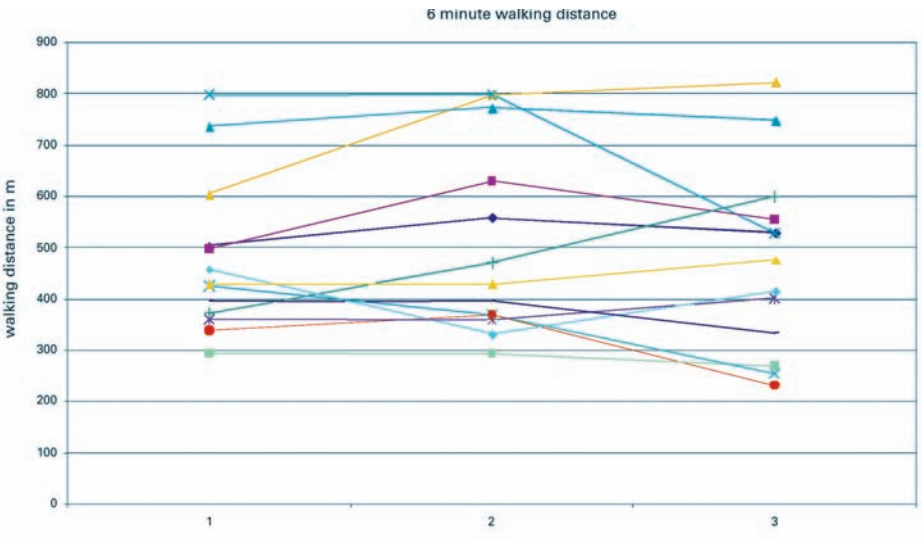

Figure 1

Changes in 6 minute walk distance in patients who did at least 3 tests (first, best and last). First test was not always at baseline examination.

Results

During the 7-year observation period 23 paediatric patients were included in the Swiss PAH registry. The gender distribution was 12 male and 11 female patients. Age at the time of diagnosis of pulmonary arterial hypertension was 1 month to 18 years, with a median of 3 years. The follow-up period was 1 day to 12.6 years with a median of 3.47 years.

Of these 23 patients all but one are alive. One patient died before treatment was instituted.

The aetiology of PAH was idiopathic in 8/23 patients (34.8%). PAH associated with congenital heart disease (CHD) with left-to-right shunt was found in 12/23 patients (52.2%) and associated with a pulmonary disease in 3/23 patients (13.0%).

Patients with CHD displayed the following cardiac malformations: transposition of the great arteries (TGA) with additional ventricular septal defect (VSD) in 2/12 patients, aortopulmonary window in 1/12 patients, atrioventricular septal defect (AVSD) in 1/12 patients, VSD in 4/12 patients, atrial septal defect (ASD) of the superior sinus venosus type in 1/12 patients and patent arterial duct (PDA) in 1/12 patients. Down syndrome was diagnosed in 3/12 children (1 with AVSD, 2 with VSD). Heart surgery was performed in 6/12 children. In 2 children PAH was not present before surgery, 3 had PAH which was not considered fixed PAH and 1 patient had fixed PAH. In this patient a palliative Senning operation was performed to help decrease hypoxaemia and enhance quality of life. 6/12 children had marked pulmonary vascular disease and they were not considered suitable for cardiac surgery (table 1).

By the end of the observation period all the paediatric patients alive were on a specific treatment. 12/22 patients were on a single medication and 10/22 on combined medications. Single treatments included calcium channel blocker in 2/22 patients, the dual endothelin receptor blocker bosentan (Tracleer®) in 9/22 patients, and inhaled iloprost (a prostacyclin analogue) in 1/22 patients. Combined treatments included bosentan and inhaled iloprost in 6/22 patients, bosentan and sildenafil (a phosphodiesterase type V inhibitor) in 2/22 patients, and bosentan, sildenafil and inhaled iloprost in 2/22. 14/22 patients were on oral anticoagulation and 8/22 received oxygen therapy.

The functional classes were assessed in 22/23 patients at their first visit. 4/22 patients were in NYHA Class 2, 17/22 in NYHA Class 3, and 1/22 in NYHA Class 4. Over a period of 2 years 3/22 patients changed NYHA class from class 3 to class 2.

Exercise capacity was assessed by 6-minute walk distance, which was measured according to the ATS Guidelines [5]. Interpretation of this test is difficult during childhood, however, since no normal values exist for age and gender, especially in small children. In some patients baseline values are lacking due to their too young age at baseline examination. Nevertheless, in 6/13 patients an initial improvement in 6-minute walk distance was noted and in 4 patients this improvement was sustained (fig. 1).

Discussion

These paediatric data are the first data to be extracted from the Swiss Registry for PAH. Because of the small number of patients, only a descriptive analysis of the epidemiological data was performed. Nevertheless, these data are the first available information on the epidemiology of PAH in the paediatric population of a single country.

The data collected are very heterogeneous. This may be related to the different aetiologies of PAH entered in the registry and may be specific to paediatric PAH. Some data were entered retrospectively and this also explains the heterogeneity, since not all data were available for all patients.

The therapies in use at the end of the follow-up period and their combination were highly heterogeneous. A possible explanation is the time when the children were included, a period in which several new therapies became available and thus were introduced into the paediatric therapeutic armamentarium. In the beginning only calcium channel blockers and prostacyclin analogues were available. Bosentan and sildenafil became available during the follow-up period. In the results presented only the therapies at the end of the follow-up period are described. During follow-up therapy was adapted or added according to the patients' clinical evolution.

During the follow-up period only 1 patient died. This suggests that survival has improved under the therapies presently in use, as compared to data published 16 years ago [3].

The data show that many patients undergo stabilisation of their disease under the currently available treatments [6]. A few patients even showed some improvement in their functional and exercise capacity.

However, interpretation of exercise capacity by 6-minute walk distance remains difficult in children. No normal values currently exist, especially for small children [7]. Hence the 6-minute walk distance of a child with PAH cannot be reli-

ably compared with values in healthy children of the same age group. Further, in children the 6-minute walk distance most probably depends on age, height, weight, muscle mass and body mass index, and will change as childhood advances. In adults too it has been shown that walk distance is dependent on age, weight and height [8]. Thus an improvement in walk distance in children with PAH cannot be ascribed to successful treatment alone. However, the results of serial 6-minute walk tests in a single patient can provide information on stabilisation or deterioration of the disease course, and thus may be highly informative and helpful during follow-up of a single patient.

A 6-minute walk test was not possible in all children, the main limitation being the minimum age at which a 6-minute walk test can be performed (approximately 4–5 years). Moreover, in some children PAH was diagnosed and treatment initiated before they could walk. The 6-minute walk test was therefore interpreted in patients who had done at least 3 tests.

The patients entered in our registry display PAH of three different aetiologies, congenital heart disease with left-to-right shunt, idiopathic, and associated with pulmonary disease. Patients with unoperated congenital heart diseases presenting with Eisenmenger syndrome appear to have a different disease course with better survival [9, 10]. On the other hand, patients with an underlying congenital lung disease and in many cases malformations of the lung tissue appear to have a poorer outcome and a lesser response to medical therapies. Data emerging from the registry in the future may provide detailed information on the outcome of PAH of different aetiologies.

Data from registries for rare diseases may provide important information concerning not only currently available but also newly licensed therapies. In the future the use of a registry of this kind may also help to improve the overall medical management of paediatric PAH.

Correspondence:
Dr. med. Margrit S. Fasnacht
Paediatric Cardiology
University Children's Hospital Zurich
Steinwiesstr. 75
CH-8032 Zurich
E-Mail: margrit.fasnacht@kispi.uzh.ch

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