Clinical Characterization of Pediatric Pulmonary Hypertension: Complex Presentation and Diagnosis

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Objectives To describe the clinical presentation of pediatric pulmonary arterial hypertension (PAH) and the intricacies of how to classify pediatric PAH according to the Venice classification.

Study design Children (n = 63) seen at a national referral center for pediatric PAH underwent a diagnostic work-up for diagnosis of pulmonary hypertension (PH) and associated conditions and for assessment of the explanatory role of associated conditions for the PH. Subsequently, PH was classified.

Results In 18 patients (29%), no associated conditions were identified; they were classified as having idiopathic PAH. In 45 patients (71%), ≥1 associated conditions were detected: congenital heart defects (CHD, n = 40), connective tissue disease (CTD, n = 2), disorders of respiratory system and/or hypoxemia (RSH, n = 17), and chronic thromboembolic disease (CTE, n = 1). Patients were classified according to the condition judged to be primarily explanatory for the PH. In 11 of 45 patients with associated conditions, the PH was not sufficiently explained by these conditions; these patients were classified as having idiopathic-like PAH. In 17 of 40 cases of CHD and 9 of 17 cases of RSH, these conditions were not sufficiently explanatory for the PH. Syndromal abnormalities were frequent (43%). Ultimately, classification revealed idiopathic (-like) PAH (n = 29; 46%), PAH-CHD (n = 23; 37%), PAH-CTD (n = 2; 3%), PH-RSH (n = 8; 12%), and CTE-PH (n = 1; 2%).

Conclusion Pediatric PH frequently presents with associated conditions and syndromal abnormalities. However, detailed evaluation of this complex presentation reveals that associated conditions are not always explanatory for the PH. *(J Pediatr 2009;155:176-82)*.

Pulmonary hypertension (PH) is defined by an increased mean pulmonary arterial pressure >25 mm Hg at rest or >30 mm Hg during exercise. The Venice classification categorizes 5 classes of PH on the basis of shared similarities in pathophysiological mechanisms, clinical course, and therapeutic options. Class 1 comprises pulmonary arterial hypertension (PAH). Classes 2 to 5 consist of PH associated with these conditions: pulmonary venous hypertension; disorders of respiratory system and/or hypoxemia (RSH); thromboembolic disease; and a variety of conditions termed as miscellaneous. PAH distinguishes itself from the other 4 classes of PH histologically by characteristic pulmonary vascular lesions and clinically by its chronic progressive course and response to advanced medication. PAH is subclassified into idiopathic PAH (either sporadic or familial), and PAH associated with various underlying conditions.[1,2]

Pediatric PAH is a serious fatal disease, which requires treatment with specific advanced medication. This is in contrast to other pediatric PH subclasses, in which relief of underlying conditions is the first aim. The Venice classification has proven to be useful for the diagnosis and treatment of patients with PH, because prognosis and treatment strategy heavily depend on the subclass of PH.[2] Therefore, it is important to diagnose associated conditions accurately, to assess their explanatory role in the development of PH accurately, and to subsequently classify PH accurately. However, no studies exist which describe the complex clinical decisions surrounding this diagnostic process. Data on the clinical presentation of pediatric PH are scarce and limited to studies on the outcome of children after treatment with certain medications. Thorough information about the diagnostic process before the start of treatment is lacking.[3-6]

ASD	Atrial septal defect
BMPR2	Bone morphogenetic protein receptor type 2
CHD	Congenital heart disease
CTD	Connective tissue disease
CTE	Chronic thromboembolic disease
PAH	Pulmonary arterial hypertension
PDA	Patent ductus arteriosus
PH	Pulmonary hypertension
RSH	Disorders of respiratory system and/or hypoxemia
TcSO2	Transcutaneous oxygen saturation
VSD	Ventricular septal defect

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The objectives of this study were to describe the clinical presentation of pediatric PH in a cohort of children seen at a national referral center for pediatric PAH and to describe the intricacies of how to classify pediatric PH according to the Venice classification.

Methods

In the Netherlands, pediatric cardiologic care is centralized within 8 university medical centers. Patients with suspected PH are seen by pediatric cardiologists at any of the 8 centers for initial diagnostics. The care for pediatric patients with PAH is united in a national Network for Diagnosis and Treatment of Pediatric PAH. This network includes all 8 university medical centers, 1 of which serves as an expert center. All pediatric patients suspected to have PAH are referred to this expert center for diagnostic work-up and initiation of therapy. Also, all patients with PH suspected to be caused by thromboembolic disease, miscellaneous disorders, or both (Venice classes 4 and 5, respectively) are referred to the expert center. In contrast, patients with other forms of PH, caused by pulmonary venous hypertension or caused by RSH, such as bronchopulmonary dysplasia (Venice classes 2 and 3, respectively) are not systematically referred to the expert center. The expert center has served as a referral center for pediatric PAH since 1993. In the Netherlands, the importance of centralizing the care for pediatric patients with PAH, because of the complexity of the disease and the small number of patients, has been recognized relatively early. Therefore, the expert center evolved into the national referral center for pediatric PAH, and a national network was installed during the late 1990s.

Between 1993 and 2007, a cohort of 63 children with suspected PAH was referred to the expert center. Patient data were entered in a database with informed consent from the parents/caregivers. Institutional review board approval was obtained for the registry of these patients.

At presentation at the expert center, all children underwent diagnostic work-up to diagnose PH, to identify associated conditions, and to assess the explanatory role of the associated conditions. Subsequently, PH was classified according to the Venice classification. The diagnostic work-up included standardized Doppler echocardiography and cardiac catheterization to confirm the diagnosis of PH and to systematically assess the heart for cardiac anomalies, right and left ventricular function, and to exclude pulmonary venous obstruction, left heart disease, or both. In addition, acute pulmonary vasodilator response was tested by using inhaled oxygen, nitric oxide, and/or intravenous prostacyclin. Responders were identified according to criteria as defined by Barst.[7] Diagnosis of PH was made invasively during cardiac catheterization and measurement of a mean pulmonary arterial pressure >25 mm Hg and pulmonary capillary wedge pressure <15 mm Hg at rest in 57 patients. In the 6 remaining patients, cardiac catheterization data were not available. Clinical instability (n = 4) and positive response of PH to adequate treatment of the associated condition (obstructive breathing, n = 2) were reasons for not performing cardiac catheterization in these patients. In 3 of these 6 patients who had systemic-to-pulmonary shunt related PAH, a right-to-left shunt was measured echocardiographically, establishing Eisenmenger syndrome physiology. In the other 3 patients, the presence of PH was established by measurement of a maximum systolic tricuspid regurgitant velocity >2.8 m/s, according to criteria as defined by McQuillan et al.[8]

Diagnostic evaluation for associated conditions was performed uniformly, according to protocol, in all patients, and included assessment of chest radiography, complete blood and platelet count, thyroid function, thrombotic status, human immunodeficiency virus serology, overnight oxymetry, arterial blood gas, pulmonary perfusion scanning, and screening for connective tissue disease. In selected patients, additional blood clotting studies, polysomnography, pulmonary function testing, and thoracic computed tomography scan were performed. From 2002, incident and prevalent patients with idiopathic PAH were screened for bone morphogenetic protein receptor type 2 (BMPR2) gene mutations. Clinical patient characteristics included symptoms, transcutaneous oxygen saturation (TcSO2) and World Health Organization functional class.

Data are presented as means plus or minus SD or medians and ranges, as appropriate. To analyze differences in baseline characteristics in PH (sub)classes, 1-way analysis of variance with Bonferroni post-hoc testing (TcSO2, hemodynamics) and Kruskal-Wallis followed by Mann-Whitney post-hoc testing with Bonferroni correction (symptoms, World Health Organization functional class) were performed. For 1-way analysis of variance and Kruskal-Wallis testing, (sub)classes comprising only 1 patient or only 1 available assessment were excluded. P values $<.05$ were considered to be significant.

Results

Exercise-induced dyspnea was the most common presenting symptom (98%; **Table I**). Syncope occurred in 8 patients (13%). One patient had no symptoms on presentation and was referred for screening because of a diastolic murmur and Noonan syndrome. The murmur originated from a mild pulmonary regurgitation jet with high maximal velocity.

In 45 patients (71%), ≥1 associated conditions were detected: 1 associated condition in 30 patients (48%) and 2 associated conditions in 15 patients (24%). Associated conditions consisted of congenital heart defects (CHD) in 40 patients (63%), RSH in 17 patients (27%), connective tissue disease (CTD) in 2 patients (3%), and chronic thromboembolic disease (CTE) in 1 patient (2%; **Figure 1**; available at www.jpeds.com). In 18 patients (29%), no associated conditions were identified, and these patients were classified as having idiopathic PAH (**Figure 1**). In these patients, intrinsic pulmonary vascular disease was considered to be the explanation for the PH. Patients with >1 associated condition were classified according to the associated condition judged to