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Non-congenital heart disease associated pediatric pulmonary arterial hypertension

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ABSTRACT

Recognition of causes of pulmonary hypertension other than congenital heart disease is increasing in children. Diagnosis and treatment of any underlying cause of pulmonary hypertension is crucial for optimal management of pulmonary hypertension. This article discusses the available knowledge regarding several disorders associated with pulmonary hypertension in children: idiopathic pulmonary arterial hypertension (IPAH), pulmonary capillary hemangiomatosis, pulmonary veno-occlusive disease, hemoglobinopathies, hepatopulmonary syndrome, portopulmonary hypertension and HIV. Three classes of drugs have been extensively studied for the treatment of IPAH in adults: prostanoids (epoprostenol, treprostinil, iloprost, beraprost), endothelin receptor antagonists (bosentan, sitaxsentan, ambrisentan), and phosphodiesterase inhibitors (sildenafil, tadalafil). These medications have been used in treatment of children with pulmonary arterial hypertension, although randomized clinical trial data is lacking. As pulmonary vasodilator therapy in certain diseases may be associated with adverse outcomes, further study of these medications is needed before widespread use is encouraged.

1. Idiopathic pulmonary arterial hypertension

Idiopathic pulmonary arterial hypertension (IPAH), previously called primary pulmonary hypertension, is a diagnosis of exclusion. The natural history if IPAH in children is poor. Data from 1965 revealed that 22 of 35 children diagnosed with IPAH died within 1 year of diagnosis [1]. In the NIH registry, the median untreated survival for children after diagnosis was reported to be 10 months as opposed to 2.8 years for adults [2]. This poor prognosis without targeted therapy was recently confirmed [3]. Advances in the understanding of the pathobiology of idiopathic pulmonary arterial hypertension has led to new treatment therapies and have resulted in an improvement in the prognosis for children with IPAH [4,5]. As IPAH still has no cure, the aim of treatment is to improve quality of life, hemodynamics, exercise capacity, and survival. Medical management of children follows a similar algorithm to that of adults treated with idiopathic pulmonary vascular disease [6]. Children appear to be more reactive to acute vasodilator testing compared with adults [7], and may have a better long-term outcome in the current era than adults (Fig. 1) [8].

1.1. Definition

Pulmonary arterial hypertension is defined as a mean pulmonary arterial pressure greater than 25 mm Hg at rest, with a normal pulmonary capillary wedge pressure of less than 15 mm Hg and an increased pulmonary vascular resistance greater than 3 Wood units·m^2 [9,10]. The Venice classification scheme, established in 2003 at the Third World Symposium on Pulmonary Arterial Hypertension is appropriate for adults and children. This classification has recently been updated at the Dana Point, California Fourth World Symposium on Pulmonary Arterial Hypertension [11]. Exercise criteria have been deleted for the current definition [10]. The diagnosis of IPAH is one of exclusion and therefore requires a complete evaluation of all possible etiologies of associated pulmonary arterial hypertension, left heart disease, and respiratory disease [10,12]

1.2. Heritability

Bone morphogenetic protein receptor type 2 (BMPR2) mutations have been identified in children and adults with IPAH and familial PAH [13–18]. This genetic mutation in the TGF-Beta receptor has been found in patients with familial PAH (50%) [17] and sporadic PAH (15–26%) [18]. BMPR2 mutations are inherited as in autosomal dominant pattern with reduced penetrance and genetic anticipation. In many families, it is the child who presents first with severe disease, and then further evaluation of first degree relatives reveals milder disease in the parents or grandparents [19]. In children, BMPR2 mutations have been evaluated with inconsistent results. Grunig found no BMPR2 mutations or deletions in 13 children with idiopathic pulmonary arterial hypertension [16]. However, in a study by Harrison et al., 22% of children with IPAH or pulmonary hypertension associated with congenital heart disease had activin-like kinase type-1

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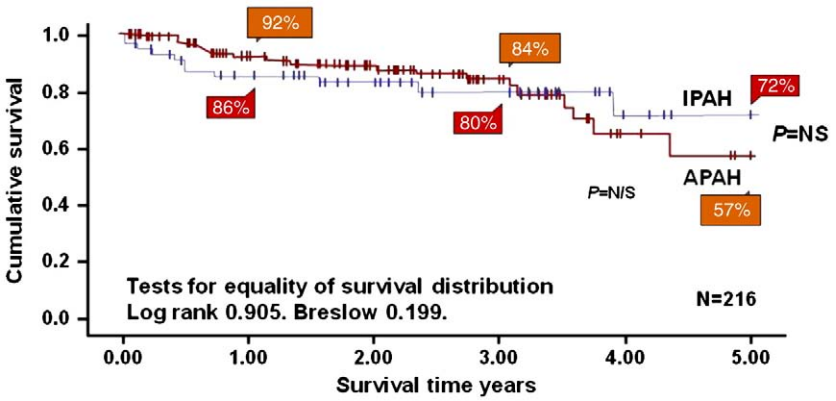

Fig. 1. Kaplan–Meier survival curve of children with idiopathic pulmonary arterial hypertension (IPAH) and associated pulmonary arterial hypertension (APAH) from the UK Pulmonary Hypertension service from 2001–2007.
Haworth and Hislop. Heart 2009;95:312–317.

(ALK-1) or BMPR2 mutations [15]. More recently, a study by Rosenzweig et al. evaluated whether children and adults with pulmonary arterial hypertension had a positive response to acute vasodilator testing, and found that BMPR2 mutation positive children appeared less likely to respond to acute vasodilator testing than mutation negative children [20]. These findings are similar to those by Elliott et al. who reported that IPAH and FPAH adult patients with BMPR2 mutations are less likely to respond to acute vasodilator testing than BMPR2 mutation negative patients [21]. A study from Japan suggested that mutations of the activin receptor-like kinase 1 gene in addition to bone morphogenetic protein receptor II gene may be important in the development of IPAH in children [22].

Other genetic loci may also play important roles. Studies have shown mutations of the serotonin transporter gene in some adults with PAH [23], and a study in children found that homozygosity for the long variant of the serotonin transporter gene was highly associated with idiopathic pulmonary hypertension in children [24]. Chung et al. demonstrated an association of a polymorphism in the angiotension II type 1 receptor (AGTR1) with the age at diagnosis of pulmonary hypertension [25]. Future genetic studies may provide further insight regarding disease severity and age of onset in children.

1.3. Evaluation

A complete evaluation for all possible causes of PAH is required before the diagnosis of IPAH is made. Certain diseases, such as connective tissue disease or chronic thromboembolic pulmonary hypertension, are less likely to be discovered in children than adults, but still should be excluded. Cardiac catheterization is required to rule out subtle congenital heart disease, such as pulmonary vein disease, to determine right atrial pressure, exact pulmonary arterial pressure, pulmonary vascular resistance, and to determine vasoreactivity to acute vasodilator testing to target therapy. Lung biopsy is rarely performed but may be helpful to exclude certain diseases, such as pulmonary veno-occlusive disease, pulmonary capillary hemangiomatosis or alveolar capillary dysplasia (see below). Furthermore, in certain forms of interstitial lung disease, such as pulmonary capillaritis or hypersensitivity pneumonitis, lung biopsy may be beneficial as treatment of these disorders varies markedly from the approach used in IPAH.

As in adults, the 6-minute walk test is feasible and has been used to measure sub maximal exercise. Unfortunately, the 6 MW test has not been validated in children with PAH, but normal values in children have recently been described [26]. Children with pulmonary hypertension have significant impairment in aerobic capacity, with a peak oxygen consumption of 20.7 ± 6.9 versus 35.5 ± 7.4 ml/kg/min in healthy controls ($p < 0.0001$) [27].

Interest in biomarkers has grown in the last several years. In adults, brain natriuretic peptide (BNP) is a useful tool to assess mortality risk, progression of the disease and response to therapy [28,29]. Recent studies in children have begun to identify usefulness

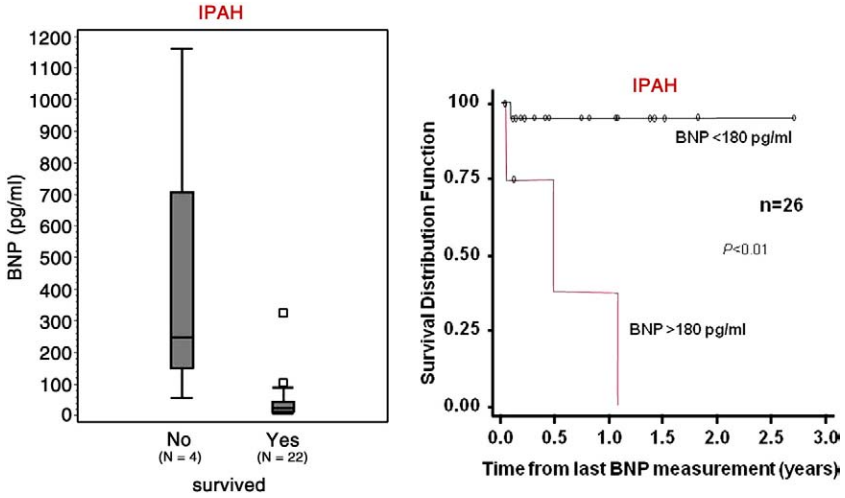

Fig. 2. Differences in the last observed brain natriuretic peptide (BNP) distributions between survivors and nonsurvivors for IPAH patients (A). Kaplan–Meier curves estimating cumulative survival for IPAH patients categorized with either high BNP (>180 pg/ml) or normal (<180 pg/ml).
Bernus, A. et al. Chest 2009;135:745–751.