

## CURRENT TOPIC

## Primary pulmonary hypertension in childhood

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This is an opportune time to reappraise primary pulmonary hypertension. The disease is still incurable but recent laboratory studies are beginning to provide clues to its pathogenesis, and we now know that survival is improved by sustained intravenous prostacyclin treatment and by chronic anticoagulation. In 1991, before these treatments were generally available, the median survival was given as 2.8 years, based on the National Institute of Health Registry.<sup>1</sup> In patients with a cardiac index of less than 2 l/min/m<sup>2</sup>, the median survival was 17 months, and untreated patients with a right atrial pressure exceeding 20 mm Hg lived for one month. Recent reports show a 49% survival rate at 30 months and a 25% survival rate at five years in older children and adults treated with continuous intravenous prostacyclin.<sup>2</sup> Survival is better in younger children.<sup>2</sup> In general, the disease is similar in adults and children but there are important differences.

Primary pulmonary hypertension is diagnosed when there is no explanation for the increase in pulmonary arterial pressure. The mean pressure exceeds 25 mm Hg at rest and 30 mm Hg on exercise. The disease is progressive, leading to a gradual increase in right ventricular pressure, right heart failure, functional incapacity, and death. In 1975, a WHO committee defined primary pulmonary hypertension according to morphological criteria, as being caused either by pulmonary arterial obstruction (the commonest pathology), pulmonary veno-occlusive disease, or thromboembolism. This unsatisfactory definition will be revised later this year. Persistent pulmonary hypertension of the newborn is excluded from this diagnostic group, although in some young patients with primary pulmonary hypertension the pulmonary circulation might have failed to grow and develop normally. In most patients with primary pulmonary hypertension, adults and children, the organisation of elastin in the pulmonary trunk indicates that pulmonary hypertension was not present from birth. Including all ages, the incidence of primary pulmonary hypertension is approximately 1-2/1 000 000 in Western countries.<sup>1</sup> In the Indian subcontinent, children suffer from a particularly vicious form of the disease, but the incidence of primary pulmonary hypertension in children of Indian origin living in this country is no greater than that of the native population. Women are more frequently affected than

men, and recent studies show that a female preponderance is present from early childhood.<sup>3</sup> Most cases are sporadic, but 6% are familial.<sup>4-5</sup> (I know of 10 affected families in the UK.) The disease is inherited in an autosomal dominant manner, with incomplete penetrance.<sup>5-6</sup> Familial primary pulmonary hypertension shows gene anticipation, presenting at a younger age in successive generations.<sup>7</sup> Recent studies have located a gene for familial primary pulmonary hypertension to chromosome 2q 31-32.<sup>8</sup>

### Pathology and pathogenesis

At postmortem examination, most adult cases are characterised by advanced pulmonary vascular obstructive disease with plexiform lesions. This picture is also common in older children and can be seen before 3 years of age. However, severe pulmonary arterial medial hypertrophy with marked intimal proliferation can also occur, and is seen more commonly in young children. The changes can be so exuberant and rapidly progressive that the lumen becomes obstructed before intimal fibrosis and plexiform lesions have had time to develop. Such cases, showing medial hypertrophy and cellular intimal proliferation, rather than fibrotic obstruction with dilatation lesions, might be particularly amenable to vasodilator treatment.

The pathogenesis of primary pulmonary hypertension is unknown. The evidence suggests that it is a disease of individuals with a genetic predisposition to respond adversely to a variety of stimuli, the response initiating a cascade of events leading to the development of pulmonary vascular disease. The clinical and structural findings represent the final common pathway. Likely triggers include drugs, particularly anorexic agents such as fenfluramine, dexfenfluramine, and aminorex<sup>9-10</sup>; toxins; hypoxia, including high altitude hypoxia; lung injury; catecholamine induced increases in sympathetic tone; and autoimmune diseases, such as disseminated lupus erythematosus.<sup>11-12</sup> Unlike adults, young children do not show an increased incidence of antinuclear antibodies, but their healthy mothers do, and some children seroconvert when they are older.<sup>3</sup> Most autoimmune diseases are associated with an increase in certain human leucocyte antigen (HLA) class II alleles, and children with primary pulmonary hypertension have an increased frequency of HLA DR3,

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HLA DR52, and HLA DQ2.<sup>13</sup> Primary pulmonary hypertension does not occur in the transplanted lung, suggesting that it is a disease intrinsic to the pulmonary circulation, not just a response to an abnormal/excessive circulating product.

Intense vasoconstriction is thought to be the common early response to injury. Recent experimental studies show that, like hypoxia, the anorexic agents that cause primary pulmonary hypertension inhibit potassium current in the smooth muscle cells of pulmonary resistance arteries, causing membrane depolarisation and hence vasoconstriction.<sup>14</sup> The endothelium probably plays a crucial role in the pathogenesis of the disease, influencing both vasoconstriction and structural remodeling, functions which are inseparable. Vasoconstrictor agents such as endothelin are also vascular smooth muscle mitogens, while vasodilator agents such as prostacyclin and nitric oxide can be antiproliferative and antimigratory. Two of the most powerful intrinsic vasodilators are thought to be deficient in patients with primary pulmonary hypertension, prostacyclin and nitric oxide. The amount of exhaled nitric oxide is normal at rest but fails to increase on exercise.<sup>15</sup> This probably reflects both endothelial dysfunction and the reduction in endothelial surface area that occurs with advancing obstructive disease. Other metabolic indicators of endothelial dysfunction include an excess of circulating thromboxane in relation to prostacyclin, raised endothelin concentrations, and coagulation abnormalities.<sup>16-17</sup> The role of platelet aggregation in the pathogenesis of primary pulmonary hypertension is unknown, but raised fibrinopeptide A concentrations indicate that thrombosis occurs in situ, and thrombosis is frequently evident in the established disease seen at necropsy.<sup>18</sup> An abnormally high release of serotonin from aggregating platelets is thought to account for the raised plasma serotonin concentrations found in these patients.<sup>19</sup> Anticoagulation treatment increases survival.<sup>20</sup> The rationale for giving chronic vasodilator treatment is that a reduction in vasoconstriction will not only alleviate symptoms but will retard the progression of vascular disease from medial hypertrophy to plexogenic arteriopathy. This applies particularly to chronic intravenous prostacyclin treatment.

### Clinical features

Patients can present throughout childhood. Symptoms vary and are age related. Some children are considered to have been normal, others fail to thrive, are thought to have epilepsy, or present with syncope, sometimes fatally. Older children, like adults, have exertional dyspnoea and might have chest pain. Evaluation includes exclusion of other causes of pulmonary hypertension, primarily cardiac, and screening other siblings for the familial form of the disease. In general, echocardiography reveals dilated right heart chambers, with posterior bowing of the ventricular and, in the absence of a small atrial communication, the atrial septum. Doppler interrogation detects

tricuspid and pulmonary insufficiency and the velocity of the regurgitant jets gives an estimate of the pulmonary arterial pressure. Lung function testing can demonstrate small airways obstruction and, according to Mikkilineni *et al*,<sup>21</sup> the degree of obstruction correlates with the degree of symptomatology and the haemodynamic findings.<sup>21-22</sup> On exercise testing, an exercise capacity of more than 75% of the predicted value might identify those patients likely to respond well to vasodilator treatment.<sup>22</sup> All these non-invasive tests are important not only in diagnosis but in monitoring the progression of the disease and the effect of treatment. In addition to the association between primary pulmonary hypertension and autoimmune disease, familial primary pulmonary hypertension can be associated with immunoglobulin isotype deficiencies,<sup>23</sup> and pulmonary hypertension has been reported in patients with human immunodeficiency virus infection.<sup>24</sup> There might also be a low concentration of antithrombin III, protein S, or protein C, which might be genetic in origin, or result from a consumption coagulopathy.<sup>25</sup>

The cardiovascular system is very brittle in these children and cardiac catheterisation is hazardous. Adequate sedation, optimal ventilation, and meticulous attention to acid base status and blood loss is mandatory. The pulmonary arterial pressure, vascular resistance, and cardiac index are higher in children than in adults presenting with primary pulmonary hypertension, and in one study these measured 70 (15) mm Hg, 28.1 (18.1) units/m<sup>2</sup>, and 4.3 (3.9) l/min/m<sup>2</sup>, respectively (mean (SD)).<sup>3</sup> Taking an open lung biopsy is also not without risk but, when the clinical picture is uncertain, a biopsy can be invaluable in excluding other pathologies before embarking on long term treatment.

### Treatment

Treatment for primary pulmonary hypertension is treatment for life. The therapeutic regimen has to be tailored to meet the needs of each individual, and adjusted as and when required, according to changes in clinical and haemodynamic status. Optimising the management of these patients greatly improves quality of life and survival. Conventional treatment of children with primary pulmonary hypertension in the UK consists of giving anticoagulants and oral vasodilator treatment, usually a calcium channel blocker, and supplemental domiciliary oxygen.<sup>26</sup> Warfarin rather than aspirin or dipyridamole is recommended to prevent thrombosis in situ.<sup>20</sup> The desirability of using chronic vasodilator treatment is assessed at cardiac catheterisation by the acute response to a vasodilator drug. Chronic vasodilator treatment can have an adverse effect and precipitate or worsen right heart failure in children with unfavourable haemodynamics, who have a high fixed pulmonary vascular resistance. Drugs used for testing responsiveness include acetylcholine, nitric oxide, adenosine, and prostacyclin. Acute responsiveness to prostacyclin is assessed by giving incremental doses of the drug, from 2–12 ng/kg/min, or more.<sup>3</sup> Children

tolerate higher doses of prostacyclin than adults. A positive response to a vasodilator is taken as a decrease in mean pulmonary arterial pressure of 20% or more, with no fall in cardiac index. The positive response rate to acute vasodilator testing with orally administered vasodilator drugs is higher in children than in adults, 41% compared with 12%.<sup>27</sup>

Only 40% of children showed a clinical and haemodynamic improvement and lived longer when treated with oral vasodilator treatment.<sup>27</sup> Recent studies have shown that chronic intravenous prostacyclin treatment is more effective.<sup>2, 28, 29</sup> A study by Barst and colleagues<sup>2</sup> reported a five year survival of 88% in children less than 6 years of age, as compared with 25% for older children.<sup>30</sup> The most important determinants of survival are age and the acute response to prostacyclin. In a group of children who responded satisfactorily to acute prostacyclin at catheterisation, the five year survival was 86% compared with 33% for non-responders.<sup>2</sup> Some patients who do not respond to acute vasodilator treatment can respond satisfactorily to chronic treatment, but need close supervision. Also, some patients who do not respond to oral chronic vasodilator treatment can be treated with intravenous prostacyclin, to good clinical and haemodynamic effect, with increased survival.<sup>31</sup> Unfortunately, there is no evidence that prostacyclin given by inhalation is as effective as giving the drug intravenously in this disease. Despite the obvious logistical problems, infants and young children can be managed satisfactorily on a continuous infusion of prostacyclin. Children of all ages have been treated, from as young as 2 months.<sup>27</sup> Problems include abrupt interruption of the infusion, which is usually noticed very rapidly, causing fatigue and occasionally syncope.<sup>27, 29</sup> Rarely, death supervenes, presumably as a result of a pulmonary hypertensive crisis. Less dramatic complications include discomfort at the catheter site, bleeding, infection, and thrombotic episodes. Patients can become very tolerant of prostacyclin, requiring constant, aggressive, upward adjustment of their dosage. In general, clinical and haemodynamic improvement is sustained. Some patients given prostacyclin as a bridge to transplantation have improved to such an extent that they are being treated with intravenous prostacyclin long term, rather than being transplanted.<sup>3, 28</sup> In these patients, prostacyclin appears to be acting primarily by structurally remodelling the pulmonary vasculature, rather than acting as a pulmonary vasodilator.<sup>28, 32</sup> While the reduction in pulmonary vascular resistance achieved by long term calcium channel blockers does not increase with time, a study published in January 1998 demonstrated that long term intravenous prostacyclin treatment achieves a greater reduction in resistance than is achieved at the outset by acute vasodilator testing.<sup>28</sup> Treatment should be continued indefinitely.

Atrial septectomy has been carried out in children with primary pulmonary hypertension. It has been shown to improve survival in adults with recurrent syncope who have a poor prognosis.<sup>33</sup> In exercise induced syncope,

#### Key messages

- Greater awareness of the disease should facilitate earlier diagnosis in childhood
- Management can and should be more aggressive
- Rarity of primary pulmonary hypertension and recent advances in basic and clinical research indicate the need for closer collaboration and a UK registry of primary pulmonary hypertension
- During the next decade, the links between genetic predisposition and the cascade of cell signalling events leading to vessel wall pathology will clarify the pathogenesis of the disease and lead to improved treatment strategies

the systemic circulation dilates and cardiac output cannot be sustained. However, in the presence of a right to left shunt at atrial level, output is maintained and the right heart chambers are decompressed. Following blade atrial septectomy, the one and two year survival rates improved from 54% and 42%, respectively, to 87% and 76%, respectively. Syncope was abolished. Atrial septectomy can be used as a bridge to transplantation, and ought to be a helpful adjunct to medical treatment in children, particularly if used earlier, in less moribund patients.

Except for those children who can be managed satisfactorily on long term oral vasodilator drugs or intravenous prostacyclin, the only treatment that can be offered to patients with primary pulmonary hypertension is transplantation. Apart from the problem of graft availability, the results of transplantation are not good, making it incumbent upon us to optimise medical treatment.

#### Future developments

In the future, we would hope that genetic and molecular biological studies will help us identify children with a genetic predisposition to develop primary pulmonary hypertension, discover when and why they develop the disease, and eliminate appropriate trigger factor(s) to which the child might be exposed. For the present, early diagnosis depends upon greater awareness of the condition and of its varying modes of presentation. The improvement in quality of life and survival in patients treated with continuous intravenous prostacyclin suggests that structural remodelling of the diseased vessel wall is a realistic possibility. Therefore, the use of other vasodilator/antimitogenic mediators such as nitric oxide should be explored. Conversely, vasoconstrictors/mitogenic signalling pathways might be downregulated by—for example, endothelin receptor and/or thromboxane antagonists. It might be appropriate, costs not withstanding, to treat all patients indefinitely with prostacyclin. Alternatively, the less symptomatic children who respond to acute oral vasodilator testing might be treated with a continuous prostacyclin infusion initially, hoping to maximise any remodelling effect as early in

the course of the disease as possible, and then be transferred to oral vasodilator treatment. It is time to adopt a more positive, aggressive approach to the management of this disease in childhood.

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