Primary Pulmonary Hypertension

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Summary

Primary pulmonary hypertension (PPH) is a rare disease. The annual incidence in the West is 1-2 cases per million population per year. A recent WHO symposium in 1998 has produced a consensus on classification, methods of screening, risk assessment and treatment. PPH is a diagnosis of exclusion after all other secondary causes of pulmonary hypertension are ruled out. Current treatment strategy involves acute vasodilator drug trial where positive responders are treated with high dose calcium channel blockers and anticoagulation. Those who do not show positive response may be commenced on intravenous prostacyclin. Surgical treatment is one option for patients with severe PPH or for symptomatic relief. Prognosis in general is very poor.

Key Word: Primary pulmonary hypertension

Introduction

Primary pulmonary hypertension is a rare disorder. It was first described more than 100 years ago but the term primary pulmonary hypertension was only first used in the 50s[1]. An epidemic of pulmonary hypertension in Europe linked to the appetite suppressant aminorex fumarate prompted the first WHO sponsored symposium on PPH more than 25 years ago. In 1998 a further WHO sponsored symposium on PPH was held in Evian, France. The result of this symposium was consensus about classification of pulmonary hypertension, the pathobiological methods of screening, risk assessment and treatment.

Definition and classification

Pulmonary hypertension is defined as a mean pulmonary artery pressure (PAP) of more than 25 mmHg at rest or 30mmHg during exercise[2]. Pulmonary artery pressure is measured by right heart catheterisation study.
Primary pulmonary hypertension is diagnosed when all types of secondary hypertension have been excluded on clinical grounds.

In the past pulmonary hypertension has been classified as either primary or secondary. A new classification proposed at WHO meeting in 1998 is summarised in Appendix 1[3]. In addition, the meeting has also provided a classification of risk for pulmonary hypertension (see Appendix 2).

Epidemiology

This disorder has an incidence of one to two cases per million people per year in Western populations. The incidence is higher among appetite suppressant users (25 to 50 per million per year)[4]. The mean age of diagnosis is in the mid 30s but it can occur at any age[5]. In males the disease occurs at a slightly higher age than females. The disease ratio however favours females at a ratio of 1.7:1. Familial PPH accounts for roughly 10% of cases. Race does not appear to have any effect on risk for primary pulmonary hypertension[5].

Pathology

The pulmonary vasculature is very compliant and acts as a high flow, low-pressure system to accommodate increased cardiac output during exercise. The pathological features of PPH are not diagnostic. These include smooth muscle hypertrophy in the media, intimal hyperplasia and in situ thrombosis. Other features present include arteritis and plexogenic arteriopathy. Plexogenic arteriopathy is a form of angiogenesis in response to vascular injury in PPH. It consists of a mass of disorganised vessels associated with endothelial cells, smooth muscle and myofibroblasts.

Primary pulmonary hypertension has three distinct pathological patterns[6]: plexogenic arteriopathy (50%), thrombotic arteriopathy (40%) characterised by intimal fibrosis and recanalised in situ thrombosis and thirdly veno-occlusive disease (10%). Veno-occlusive disease is characterised by intimal proliferation and fibrosis of the intrapulmonary veins and venules. Clinical differentiation between these patterns is difficult[6]. Ventilation perfusion (V/Q) scan however may show patchy perfusion pattern in both thrombotic and veno-occlusive disease. Pathological findings in PPH may be graded according to severity of disease but has poor correlation to pulmonary artery pressure and response to vasodilators. The plexogenic pattern has the worst prognosis.

Aetiology and pathogenesis

The aetiology of PPH is not known but current understanding postulates individual susceptibility and a triggering stimulus[6]. This then initiates a complex interaction between various substances to cause pulmonary vascular injury and repair. The complex interaction favours vasoconstrictive mediators (e.g. endothelin 1) over vasodilators (e.g. nitric oxide and prostacyclin) which results in pulmonary vasoconstriction. Vasoconstriction is then followed by intimal proliferation and fibrosis, in situ thrombosis and plexogenic arteriopathy[6].

Only a small percentage of high risk individuals (appetite suppressant users and HIV positive individuals) develop pulmonary hypertension. The familial form of PPH is via vertical transmission suggesting a single dominant gene. It is not sex-linked and likely to be autosomal dominant with incomplete penetrance as it may skip generations[7]. It also exhibits genetic anticipation. The first gene ascribed to PPH (code PPH1) was localised to seven million base pairs at 2q 31-32[8].

Clinical presentation

Patients commonly present with gradual onset of exertional dyspnoea[6]. The shortness of breath is usually non-specific and thus the diagnosis is usually delayed for more than 2 years from onset of symptoms. Other symptoms include chest pain from right ventricular ischaemia, syncope or near-syncope, lethargy and peripheral oedema. Raynaud's phenomenon may occur in women and is associated with a worse prognosis. Hoarseness of voice may occur from compression of left recurrent laryngeal nerve by enlarged pulmonary artery (Ortner's syndrome). Rarely haemoptysis may occur.

Physical examination

Physical examination may reveal secondary causes for pulmonary hypertension. Systemic hypertension may indicate left ventricular systolic dysfunction. Sclerodactyly may be present to suggest scleroderma. Clubbing is not a feature of PPH and the presence indicates existence of other diseases, which may cause pulmonary hypertension.

The signs of PPH will depend on the severity of disease at presentation. Common signs include accentuated second heart sound and fourth heart sound. Right ventricular heave may be palpable if right ventricle hypertrophy is present. Neck veins may reveal prominent 'a' wave from a stiff ventricle or 'v' wave from tricuspid regurgitation. Graham Steele murmur of pulmonary regurgitation may occur with right ventricular S3 gallop indicating advance right heart failure.

Diagnostic tests

Diagnostic tests are primarily aimed at excluding secondary causes of pulmonary hypertension. Some tests

are also used to assess the extent of the disease and the response to treatment.

During the initial visit[7] blood testing should include liver and thyroid function tests, serological studies and assays for HIV antibodies. Serological studies (rheumatoid factor, antinuclear antibody and antineutrophilic cytoplasmic antibody) are done to exclude occult connective tissue disease. PPH may cause positive ANA but in low titre. Chest radiograph usually shows prominent pulmonary arteries and lungs fields are usually clear. High resolution CT may be required to exclude parenchymal lung diseases. Electrocardiograph usually shows right axis deviation, right ventricular hypertrophy and T wave inversion pattern suggesting strain.

Echocardiography helps to exclude valvular disease, left ventricular dysfunction or intracardiac shunt. In severe PPH, right heart chambers dilate with right ventricular hypertrophy and paradoxical septal movement. Transoesophageal echocardiography may also be used. Pulmonary function test may detect significant airway or parenchymal lung diseases. Severe PPH may cause a mild restrictive defect with low diffusion capacity. Arterial blood gases may show chronic respiratory alkalosis and hypoxaemia from ventilation perfusion mismatching. Cardiopulmonary exercise test may show exercise limitation with reduced maximum oxygen consumption and exaggerated ventilation. V/Q scan will exclude chronic thromboembolic disease. In PPH pulmonary angiography shows characteristic pruning of distal vessels, which is not seen in chronic thromboembolic disease. Cardiac catheterisation is the most important test to assess the right and left heart haemodynamics, the presence of shunts and vasoreactivity during acute drug trials. Most pulmonary vascular centres perform acute vasodilator testing during cardiac catheterisation. Positive response during acute drug trial predicts long term response to oral vasodilator therapy. Short acting agents such as nitric oxide, intravenous prostacyclin or adenosine are used to minimise complications during the procedure. Lung biopsy is rarely required.

Management

At present there is no cure for PPH. General measure that can be taken include limitation of physical activities to reduce symptoms. Patients should also avoid drugs that may exacerbate pulmonary hypertension. These drugs include vasoactive decongestants, cardiodepressant antihypertensives and beta-adrenergic blockers. Supplemental oxygen may be used if concentration of ambient oxygen is low. Pregnancy should be avoided with suitable methods of contraception. The oral contraceptive pill is contraindicated as it increases the risk of venous thromboembolism.

The current consensus is to treat only when the pressure is more than 30mmHg measured during catheterisation[7]. In general, all eligible patients should be adequately anticoagulated with international normalised ratio (INR) at around 2 to 3. Formal acute vasodilator drug trial will then classify patients into responders and non-responders. The responders are usually maintained on high dose calcium channel blockers in addition to anticoagulation. The patients who are non-responders will have the option of chronic administration of intravenous prostacyclin.

Calcium channel blockers

Calcium channel blockers of the dihydropyridine group have been shown to improve morbidity and mortality in patients with PPH[9,10]. Nifedipine (300mg) and diltiazem (720mg) have been used in very high doses in the treatment of PPH and their cardiodepressant effect is the primary limitation to their use. Use of high doses of these drugs should follow a formal vasodilator study where only those who respond are be commenced on therapy. Features of a positive response to acute vasodilator trial include significant reduction in PAP with unchanged or improved cardiac output and unchanged systemic blood pressure[6]. It is less clear whether increase in cardiac output without any change in PAP constitutes a positive response although symptoms may improve. Positive response occurs in only 30% of patients with PPH. Once therapy is given, these patients should be closely followed up for deterioration such as heart failure. Patients must also be

warned against abrupt withdrawal of treatment as fatal rebound pulmonary hypertension can occur. Therefore high doses of calcium channel blocker should only be given by experienced physicians in a pulmonary vascular unit.

Prostacyclin

Naturally, prostacyclin is a product of the endothelial cells and acts as a vasodilator. Continuous intravenous (IV) infusion of prostacyclin (half life 3-5min) has been shown to improve pulmonary vascular haemodynamics, improve exercise tolerance and prolong survival in severe PPH[11, 12]. Previously prostacyclin was used in patients whilst awaiting transplantation but in some patients it has become an alternative. Negative acute vasodilator testing does not exclude positive response from chronic IV prostacyclin. This is because chronic administration is believed to confer additional antiplatelet or antiproliferative properties[12]. Prostacyclin is contraindicated in patients with pulmonary veno-occlusive disease as it can cause pulmonary oedema.

Potentially fatal rebound pulmonary hypertension may result should mechanical failure occur with the delivery system causing abrupt cessation of treatment. Infection may also set in because of chronic indwelling catheter. Iloprost is similar to prostacyclin but has longer half-life. Oral beraprost (prostacyclin analogue) is not yet ready for clinical use.

Anticoagulation

Treatment with anticoagulants has been shown to increase survival in patients with PPH[13,14]. The effect is additional when combined with vasodilator treatment. The goal of anticoagulation treatment should be to achieve INR of 2-3.

Others

Patients with hypoxaemia may benefit from supplemental oxygen. Diuretics may be used to control oedema either treatment induced or due to right heart failure. Spironolactone is useful in the presence of ascites. The use of digoxin as an inotrope to counter negative inotropic effect of treatment is controversial.

Surgical treatment

Atrial septotomy (balloon or blade) can be done to increase preload to the left heart and thus increase cardiac output. Although oxygen content falls but this is offset by increase in cardiac output. This procedure can alleviate symptoms of low cardiac output such as syncope. Single lung, double lung or heart and lung transplant can be done but life expectancy is shorter than for heart, liver or kidney transplant. There appears to be little difference between one operation to another in terms of effectiveness[7].

Prognosis

Untreated, PPH has a dismal prognosis. The median survival time from a case series of 137 patients in UK was only 3.4 years[15]. The mean life expectancy from US National Institute of Health, which enrolled 200 patients with PPH, was only 2.5 years from diagnosis. In patients with PPH, stroke volume index, cardiac index, right atrial pressure and mean PAP at catheterisation are linked to survival[16]. Patients who respond to calcium channel blocker and anticoagulation treatment have 95% chance of 5-year survival[14].

Prostacyclin has also improved survival in patients who fail to respond to oral vasodilator therapy.

Conclusion

In the Western population, PPH is a rare disease and it is very likely to be so in Malaysia. Although there is as yet no pulmonary vascular unit to perform acute vasodilator drug trial, this should not hinder a proper diagnosis of PPH. With the help of cardiologists to perform right heart catheter studies, this condition can be recognised and treatment with anticoagulation instituted. The decision on commencing high dose calcium channel blocker on these patients will have to depend on a positive haemodynamic response during acute drug trial. At present this is not yet possible in Malaysia.

Appendix 1 [3]
WHO classification of pulmonary hypertension

Diagnostic classification

	Y	N	Y	N	Y	N
1. Pulmonary pulmonary hypertension.	☐	☐				
1.1 Primary pulmonary hypertension			☐	☐		
a) Sporadic					☐	☐
b) Familial					☐	☐
1.2 Related to:			☐	☐		
a) Collagen vascular disease					☐	☐
b) Congenital systemic to pulmonary shunts					☐	☐
c) Portal hypertension					☐	☐
d) HIV infection					☐	☐
e) Drugs/Toxin					☐	☐
(1) Anorexigens	☐	☐				
(2) Other	☐	☐				
f) Persistent pulmonary hypertension of thenew born			☐	☐		
g) Other			☐	☐		
2. Pulmonary venous hypertension	☐	☐				
2.1 Left sided atrial or ventricular disease			☐	☐		
2.2 Left sided valvular heart disease			☐	☐		
2.3 Extrinsic compression of central pulmonary veins			☐	☐		
a) Fibrosing mediastinitis					☐	☐
b) Adenopathy/Tumors					☐	☐
2.4 Pulmonary veno-occlusive disease			☐	☐		
2.5 Other			☐	☐		
3. Pulmonary hypertension associated with disorders of the respiratory system and/or hypoxaemia	☐	☐				
3.1 Chronic obstructive pulmonary disease			☐	☐		

3.2 Interstitial lung disease ☐ ☐

3.3 Sleep disordered breathing ☐ ☐

3.4 Alveolar hypoventilation disorders ☐ ☐

3.5 Chronic exposure to high altitude ☐ ☐

3.6 Neonatal lung disease ☐ ☐

3.7 Alveolar-capillary dysplasia ☐ ☐

3.8 Other ☐ ☐

4. Pulmonary hypertension due to chronic
thrombotic and/or embolic disease ☐ ☐

4.1 Thromboembolic obstruction of the proximal
pulmonary arteries ☐ ☐

4.2 Obstruction of distal pulmonary arteries

(a) Pulmonary embolism (thrombus, tumour).
Ova and/or parasites, foreign materials) ☐ ☐

(b) In situ thrombosis ☐ ☐

(c) Sickle cell disease

5. Pulmonary hypertension due to disorders directly
affecting the pulmonary vasculature ☐ ☐

5.1 Inflammatory ☐ ☐

(a) Schistosomiasis ☐ ☐

(b) Sarcoidosis ☐ ☐

(c) Other ☐ ☐

5.2 Pulmonary capillary haemangiomatosis ☐ ☐

Appendix 2[3]
WHO classification of risk for pulmonary hypertension

A. Drugs and toxins	Y	N	Y	N
1. Definite	☐	☐		
a) Aminorex			☐	☐
b) Fenfluramine			☐	☐
c) Toxic rapeseed oil			☐	☐
2. Very likely	☐	☐		
a) Amphetamines			☐	☐
b) L-Tryptophan			☐	☐
3. Possible	☐	☐		
a) Meta-amphetamines			☐	☐
b) Cocaine			☐	☐
c) Chemotherapeutic agents			☐	☐
4. Unlikely	☐	☐		
a) Antidepressant			☐	☐
b) Oral contraceptives			☐	☐
c) Oestrogen therapy			☐	☐
d) Cigarette smoking			☐	☐

B. Demographic and medical conditions

	Y	N	Y	N
1. Definite	☐	☐		
a) Sex			☐	☐

2. Possible. ☐ ☐

a) Pregnancy ☐ ☐

b) Systemic hypertension ☐ ☐

3. Unlikely ☐ ☐

a) Obesity ☐ ☐

C. Diseases

1. Definite ☐ ☐

a) HIV infection ☐ ☐

2. Very likely ☐ ☐

a) Portal hypertension/liver disease ☐ ☐

b) Collagen vascular disease ☐ ☐

c) Congenital systemic-pulmonary cardiac shunts ☐ ☐

3. Possible ☐ ☐

a) Thyroid disorders ☐ ☐

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MCQS for Primary Pulmonary Hypertension

1. The following statements are true with regard to primary pulmonary hypertension:
   A. Pulmonary artery pressure must be above 50 mmHg measured during exercise
   B. Lung biopsy is not required for diagnosis
   C. Incidence is 10 to 20 per million population per year
   D. Commonly affects middle age women
   E. Familial variety accounts for nearly half of cases.

2. The following risk factors are not likely to be significant in development of pulmonary hypertension:
   A. HIV infection
   B. Cigarette smoking
   C. Toxic rapeseed oil
   D. Obesity
   E. Fenfluramine

3. Symptoms and signs commonly seen in primary pulmonary hypertension include:
   A. chest pain
   B. haemoptysis
   C. clubbing
   D. positive Pemberton's sign
   E. syncope

4. The following investigations are helpful in excluding a secondary cause of pulmonary hypertension:
   A. Liver function tests
   B. Chest radiograph
   C. Bone scan
   D. Echocardiography
   E. Sleep study

5. The following statements are true regarding treatment of primary pulmonary hypertension:
   A. High dose nifedipine is beneficial in almost all patients
   B. Anticoagulation should be given to all patients unless contraindicated
   C. Intravenous prostacyclin is less useful in severe primary pulmonary hypertension
   D. Oral prostacyclin is more beneficial than digoxin as inotrope to reduce symptoms
   E. Atrial septotomy may improve syncopal attacks.