Oman Medical Journal (2012) Vol. 27, No. 1: 1-2
DOI 10. 5001/omj.2012.01

Editorial

Early Recognition and Management of Pulmonary Arterial Hypertension: A Case for Profiling

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Received: 23 Aug 2011 / Accepted: 06 Nov 2011

Pulmonary arterial hypertension (PAH) is defined as a mean pulmonary artery pressure ≥25 mmHg by right heart catheterization and a pulmonary artery wedge pressure ≤15 mmHg, indicating an absence of left ventricular dysfunction. In many patients, PAH is a progressive disease associated with morbidity and often fatal.[1] The traditional concept of primary versus secondary pulmonary hypertension has been discarded and per recent classification underlying conditions for pulmonary hypertension are classified into five groups. These include Group 1 PAH and Groups 2, 3 and 4 include categories of pulmonary hypertension secondary to left heart disease, hypoxemia and lung disease and pulmonary hypertension due to chronic thromboembolism, respectively. Group 5 includes pulmonary hypertension secondary to diseases where the pathogenesis is unclear and includes sarcoidosis, myeloproliferative disorders and other miscellaneous conditions.[1]

A number of conditions with common hemodynamic and pathological features are classified as PAH Group 1. Among these conditions, idiopathic pulmonary arterial hypertension (IPAH - previously known as primary pulmonary hypertension) is a rare disease with poor outcome in the absence of effective therapy.[1] Previous data on prognosis of IPAH from the National Institute of Health registry showed a median survival of 2.8 years.[2] At the time, the only medications available were calcium channel blockers that are effective only in a small minority of patients.[3] Compared to IPAH, which is relatively rare (5.9/million); PAH associated with other group I conditions (APAH), like systemic sclerosis, human immune deficiency virus (HIV) infection, congenital heart disease, hemolytic anemia and portal hypertension is not uncommon. The prevalence of PAH is estimated between 8 to 26.7% in patients with scleroderma 2 to 6% with portal hypertension and 0.5% among HIV patients. Up to 30% of children with congenital heart disease who do not undergo repair develop PAH.[1,3] In these conditions, the presence of PAH may be associated with devastating results and often, it is the PAH rather than the underlying condition which is responsible for morbidity and mortality. For example, although the incidence of PAH among patients who have HIV infection is 0.5%; the risk is 6-12 times higher compared to the general population and the impact of PAH is high, considering the number of HIV patients globally, and also the fact that PAH may be the direct cause for mortality in 72% of deaths.[1,3,4]

In the last decade and a half, several advances have been made in elucidating the pathogenesis, genetic associations, and most importantly in the treatment of the disease. At present, in addition to calcium channel blocker; there are several modalities of therapy available and include: oral therapies like phosphodiesterase type-5 inhibitors (Sildenafil and Tadalafil) and endothelin-receptor antagonists (Bosentan and Ambrisentan), inhalational therapy (Iloprost and Treprostinil), Infusion therapy (Epoprostenol and Treprostinil) and subcutaneous therapy (Treprostinil).[3,5] A recent meta-analysis suggested that treatment was associated with a reduction in mortality of 43%.[6] However, a recently published analysis of a large French Registry showed a 3-year median survival of 58%.[7] While there has been improvement in the management and the outcome of PAH as indicated by the meta-analysis of randomized controlled trials cited above, the overall survival is still far from satisfactory as seen in the French Registry; a 3-year median survival of less than 60% is unacceptable and more could and should be done.[6,7]

Some of the factors associated with poor survival include: complex underlying pathophysiology, rapid progression of the disease and advanced state of the disease at the time of diagnosis. Patients who have functional class symptoms New York Heart Association (NYHA) III and IV have poorer prognosis when compared to patients in class I and II,[2,3] thus timely diagnosis and intervention could be very crucial in improving survival. Unfortunately, at the time of diagnosis; about 75% of patients are usually in NYHA class III and IV.[8] Furthermore, the delay between onset of symptoms and diagnosis has been reported as 27 months in a French Registry and 2.8 years in the largest United States Registry; suggesting that there is a large window of opportunity wherein intervention could improve prognosis, hence the need to capture these patients early.[8,9]

There appear to be several reasons for the delay in diagnosis. The symptoms are nonspecific; in fact in the early stages, patients are asymptomatic and later on, dyspnea on exertion is the predominant symptom. These nonspecific symptoms frequently lead to a wide battery of tests and by the time pulmonary hypertension is suspected as an etiology, crucial time has already been lost. The etiology of the disease is diverse and patients are usually taken care

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of by specialists whose awareness of the condition may not be high. Initial clinical signs of pulmonary hypertension are subtle and not always easy to pick up. By the time a clinician is able to identify signs like elevated jugular venous pressure, pulsatile hepatomegaly or edema; the patient is in right heart failure and it is already too late. The therapy of the disease is complex, and response needs to be closely monitored, which can best be achieved at specialized centers. Management of patients in non-specialized center settings frequently leads to the initiation of inappropriate therapy like calcium channel blockers in non-responders.[10] Practice guidelines published by the American College of Chest Physicians call for early referral to a specialized center.[11]

The challenge is in diagnosing patients early and getting them to the pulmonary hypertension centers in time. The systematic screening of whole populations is not practical due to the low prevalence of this rare disease. Therefore, increased awareness of treatment options combined with active screening of patients at high risk is likely to improve survival. Screening programs have proven effective in diagnosing early stage disease in patients with sickle cell disease, systemic sclerosis and HIV.[12] It would be reasonable to consider screening certain high-risk groups, including patients with the scleroderma spectrum of diseases, systemic lupus and other connective tissue diseases, as well as HIV, 1st degree relatives with familial and idiopathic PAH, sickle cell disease, cirrhosis and patients with history of drug use. Education and improving awareness of the condition among specialists taking care of these patients is crucial. From the perspective of the primary care physician; any unexplained dyspnea, fatigue, or chest pain (non-specific symptoms of pulmonary hypertension), especially among high-risk patients should warrant a consideration of the possibility of PAH.

In patients who are at high risk or are suspected to have pulmonary hypertension, particular attention should be directed to early physical signs which include; prominent jugular "a" wave, palpable left parasternal lift, loud second heart sound, early systolic ejection click, midsystolic ejection murmur and right ventricular S4 gallop. In advanced stages, there may be signs of valvular regurgitation and right heart failure which include elevated jugular venous pressure with accentuated V waves (in the presence of tricuspid regurgitation), diastolic murmur of pulmonary regurgitation, holosystolic murmur of tricuspid regurgitation, right ventricular S3 gallop, pulsatile hepatomegaly, peripheral edema and ascites.

On a chest radiograph, features of pulmonary hypertension include enlarged main pulmonary arterial shadows and attenuation of peripheral pulmonary vascular markings; enlarged right ventricle may be recognized as loss of clear retrosternal space on lateral chest radiograph. An electrocardiograph may show signs of right ventricular hypertrophy such as: right-axis deviation, a tall R wave and small S wave with lead V1, qR complex in lead V1, rSR' pattern in lead V1, large S wave and small R wave in lead V5 or V6, S1, S2, S3 pattern and ST-T segment wave depression, and inversion may be present in the right precordial leads. Right atrial enlargement is indicated by a tall P wave ≥2.5 mm in leads II, III, and aVF and frontal P-axis of ≥75°. Chest radiograph and EKG findings should not be relied upon in diagnosing or ruling out PAH. In patients suspected to have pulmonary hypertension, an echocardiogram should be obtained as a screening tool and if echo is suggestive of pulmonary hypertension, then diagnosis needs to be confirmed with right heart catheterization. Early referral to a specialized center is recommended so that diagnosis and treatment can be initiated in a timely manner and patients can be closely monitored.

Acknowledgements

The authors reported no conflict of interest and no funding was received on this work.

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