First Reported Family of Heritable Pulmonary Arterial Hypertension in Sri Lanka- Case Report

Author's Details:
[(1)]**Madegedara Dushantha** [(2)]**Bandare Asela** [(3)]**Senevirathna Sachini** [(4)]**Nakandela Samadera** [(5)]**Rathnayake R.M.D.H** - Respiratory Unit, Teaching Hospital,Kandy ,Sri Lanka
[(1)]Consultant Respiratory Physician [(2)] [(3)]Senior Registrar in Respiratory Medicine [(4)]Resident Respiratory Physician [(5)]Research Assistant
Correspondence – **Dr Dushantha Madegedara ,dmadegedara@yahoo.com**

Abstract
Primary pulmonary arterial hypertension (PPAH) is a rare, often fatal disease characterized by elevated pulmonary pressure without secondary causes. A minority of cases of PPAH are due to heritable pulmonary arterial hypertension (HPAH). HPAH is an extremely rare autosomal dominant disease, frequently caused by mutation in BMPR2 gene. Cases of HPAH have not been reported in Sri Lanka to date. We describe a Sri Lankan family, which we consider as the first reported family with HPAH.

A 38 year old female presented with two episodes of syncope following mild exertion. She reported mild exertional breathlessness, associated with bilateral leg oedema during preceding one year. There ware evidence of pulmonary hypertension and right heart failure at examination. Severe pulmonary hypertension was noted in 2D echocardiogram. Further investigations were failed to identify secondary aetiology. Her family history was remarkable that her mother and a sibling have died prematurely at 44 and 22 years of age respectively due to pulmonary hypertension. This demonstrated the autosomal dominant pattern of inheritance suggesting HPAH. However, genetic analysis was not available to recognize mutant gene due to lack of resources. Unfortunately, she succumbed to death as a result of severe uncontrolled pulmonary hypertension in spite of medical therapy.

HPAH is an extremely rare genetic disease. Detailed family history should be obtained to avoid misdiagnosis of cases in clinical practice. It is vital to recognize HPAH for family screening and early diagnosis of asymptomatic cases.

Introduction

HPAH is an autosomal dominant disease, and recognized as an extremely rare form of pulmonary hypertension with an incidence of $1/10^5$ to $1/10^6$.(1) Familial occurrence of primary pulmonary arterial hypertension was first described by Dresdale in 1954.(2) Numerous studies have recognized many different genetic mutations responsible for HPAH, of which bone morphogenetic protein receptor type 2 gene (BMPR2) accounts for 70% of cases.(3) Mutations in activin receptor like kinase type 1 (ACVRL1 or ALK1) or endoglin genes have been identified in patients with HPAH where BMPR2 mutations are absent.(4)

HPAH has slight female preponderance, and may present at any age of life, however the mean age of presentation is 36 years.(1) Dyspnoea on excersion is the usual earliest symptom. Lower limb odema, abdominal distension, early satiety, angina and syncope may develop at the onset of right heart failure as the disease progress. (5) The clinical course of HPAH and IPAH is similar. However, onset is slightly younger and hemodynamic impairment is more severe in HPAH than IPAH.(3).

Approximately 100 families with HPAH have been identified worldwide so far.(6) However, no single family with HPAH has been reported in Sri Lanka in scientific literature. We describe the first reported family with HPAH in Sri Lanka.

Case report

A 38 year old Sri Lankan muslim female initially presented for medical evaluation with two episodes of syncopal attacks associated with exercise. She also had noticed exercise induced shortness of breath during preceding one year. Additionally, she had noticed mild bilateral ankle swelling, which was more pronounced in evening. Furthermore, her history revealed few episodes of mild haemoptysis, which were not associated with plueritic chest pain or acute worsening dyspnoea. She had never experienced chest pain, orthopnoea, paroxysmal nocturnal dyspnoea or palpitations. There was no significant cough, sputum production, wheezing, and fever or constitutional symptoms.

She was noted to have central cyanosis and mild bilateral pitting type odema during examination. A cardiovascular examination found pulse rate of 80/min and blood pressure of 90/60 mmHg. Her apex beat was in 5^{th} intercostals space, in midclavicular line, having normal character. It further revealed left sided parasternal heaving and loud pulmonary component in second heart sound. But, there were no murmurs. Her respiratory system examination was within normal limits, as were the examinations of abdomen and nervous system.

A chest radiograph showed markedly enlarged bilateral pulmonary arteries and cardiomegaly. The lung field did not show evidence of significant parenchymal lung diseases. There were marked right axis deviation with prominent R wave in lead V1 and strain pattern in anterior and inferior leads suggestive of pulmonary hypertension with right ventricular hypertrophy in electrocardiography. This was confirmed in 2D echocardiogram, which showed dilated main pulmonary trunk, right ventricle and atrium with tricuspid pressure gradient of 60 mmHg suggesting severe pulmonary hypertension.

A detailed evaluation was performed aiming at aetiology of pulmonary hypertension. History and examination was not suggestive for any connective tissue diseases. She denied drug abuse including aneroxogens.

Her spirometry, diffusion capacity of carban monoxide (DLCO) and high resolution computer tomography (HRCT) were normal. However arterial blood gas analysis revealed hypoxemia. (paO2 -43.9 mmHg, paCO2-36 mmHg, pH-7.41 and bicarbonate -25 mmol/l). 2D EHCO and transoesophageal ECHO combined with bubble contrast study excluded cardiac valvopathies and shunts. CT pulmonary angiogram, lower limb duplex scan, d-dimer, sickling test, urinary haemosiderin test, antiphospholipid antiboids excluded chronic thromboembolism. Further investigations including full blood count, sedimentation rate, renal function tests, liver profile, and ultrasound scan of abdomen, HIV antibodies, antinuclear factor, anti-ds-DNA antibodies and polysomnography did not find any abnormality. However, thyroid stimulating hormone level was marginally raised to 4.77 IU/mL (0.3-3.6 IU/mL)

Detailed inquiry into her family history unveiled that her mother and elder sister has died early at the age of 44 and 22 respectively due to a cardiac pathology. Thorough search on clinical records discovered that both patients had been diagnosed with primary pulmonary hypertension. Since autosomal dominant pattern of inheritance is demonstrated, heritable pulmonary arterial hypertension was diagnosed in this family. However, culprit genetic mutation was not able to identify due to unavailability of resources. Other family members including two brothers and a sister of the patient were screened for pulmonary hypertension with 2D ECHO, but no new cases were found. The patient expired due to uncontrolled pulmonary hypertension and right heart failure in spite of maximum medical therapy.

Discussion

Pulmonary arterial hypertension (PAH) is defined as persistently elevated pulmonary arterial pressure exceeding 25 mmHg at rest or 30 mmHg at exercise while pulmonary capillary wedge pressure and left ventricular end diastolic pressure being less than 15 mmHg.(6) PAH can be idiopathic, heritable or associated with certain conditions such as connective tissues diseases, HIV infection or portal hypertension.(5) Approximately 6% of PAH has a positive family history suggesting HPAH.(3,6)

HPAH is an extremely rare condition with an incidence of 1 in 10^5-10^6. It has an autosomal dominant type of inheritance with incomplete penetrance. Life time risk of developing disease in people with genetic mutations is 10 to 20%.(3) Females preponderance is seen with a ratio of 1.7:1 to 2:1.(1,3). Our family study too demonstrates this favorable occurrence of HPAH in females. The role of modifying genes together with environmental exposures such as hormones may account for this difference (3).

Several genetic mutations have been discovered since the first description of HPAH in 1954. Two genes in Transforming growth factor-β (TGF-β) have been strongly associated with HPAH.(6) Mutation in BMPR2 gene is found in 70% of HPAH cases. (3,4) Heterogeneous mutations in activin receptor like kinase type 1 (ACVRL1 or ALK1) or endoglin genes have been identified in patients with HPAH uncommonly(3,4) However, the responsible genetic mutation in indexed family was unable to recognized due to lack of resources.

Genetic anticipation, the occurrence of disease at younger age and with a higher severity in successive generations, is recognized in HPAH. This phenomenon was observed in our family too. However usual genetic mechanism for such phenomena is not identified in relevant genetic mutation causing HPAH. Therefore, further studies are required to delineate the process of anticipation in HPAH.(3)

Although about 100 families with HPAH found globally so far, there has been no case reported from Sri Lanka. This could be due to poor recognition of cases with PAH due to lack of facilities. Moreover, the importance of thorough clinical history should be emphasized to avoid misidentification of families with this rare condition.

Conclusion

HPAH is an extremely rare genetic condition. Clinical manifestations follow closely with IPAH. Detailed clinical history including family history should be obtained to avoid misdiagnosis of cases in clinical practice. It is vital to recognize HPAH for family screening and early diagnosis of asymptomatic cases.

References

i. *Deng Z, Morse J H, Slager S L, Cuervo N, Moore K J, Venetos G, et al. Familial Primary Pulmonary Hypertension (Gene PPH1) Is Caused by Mutations in the Bone Morphogenetic Protein Receptor–II Gene. Am J Hum Genet. 2000 Sep; 67(3): 737–744. doi: 10.1086/303059*
ii. *Girerd B, Weatherald J, Montani D, Humbert M. Heritable pulmonary hypertension: from bench to bedside. Eur Respir Rev 2017;26:170037 [https://doi.org/10.1183/16000617.0037-2017]*
iii. *Machado R D, Eickelberg O, Elliott C G, Geraci M W, Hanaoka M, Loyd J E, et al. Genetics and genomics of pulmonary arterial hypertension. J Am Coll Cardiol 2009;54:S32–42*
iv. *Montani D, Günther S, Dorfmüller P, Perros F, Girerd B, Garcia G, et al. Pulmonary arterial hypertension. Orphanet J Rare Dis. 2013: 6:97*
v. *Rich J D, Rich S. Circulation. 2014;130:1820-30*
vi. *Faber H W, Loscalzo J. Pulmonary arterial hypertension. N Engl J Med. 2004;351:1655-65*