

Possible Hereditary Pulmonary Arterial Hypertension: From Clinical to Genetic Investigation in Precision Medicine Era

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ABSTRACT

Background: Pulmonary Hypertension is a life-threatening disease characterized by a progressive increase of pulmonary vascular resistance that often leads to right ventricular (RV) failure and death. Major discoveries have been obtained within the last decade in the field of hereditary predisposition to pulmonary arterial hypertension (PAH). At least 6% of all PAH cases are familial in origin known as Familial Pulmonary Arterial Hypertension (FPAH) and display autosomal dominant inheritance with incomplete penetrance. While early diagnosis is associated with improved long-term survival, however at present, most patients are diagnosed at a very advanced stage of HPAH indicating that the early screening for HPAH is crucial. In this regard, genetic testing is an effective strategy for the early diagnosis and management of PAH, specifically Hereditary Pulmonary Arterial Hypertension (HPAH). We present two cases of Familial Pulmonary Arterial Hypertension and in-depth analysis of diagnostic cascade to allow an earlier and more reliable diagnosis of possible Hereditary Pulmonary Arterial Hypertension (HPAH).

Case Illustration: Familial cases, a 44-years old man and his son a 17-years old boy, came with chief complaint of dyspnea. His daughter or his sister passed away when 4 years old due to PH. Both patients had been subsequently diagnosed with PAH with possible HPAH after the exclusion of primary and secondary heart anomalies using electrocardiography, echocardiography, and cardiac marker test. Both patients subsequently were performed right heart catheterization (RHC).

Conclusions: We describe familial cases of pulmonary hypertension with clinically presenting right-sided heart failure. Diagnostic investigation was performed according to recent guideline to rule out and rule in all the possible cause of pulmonary hypertension. However, the final assessment showed unknown cause of pre-capillary pulmonary hypertension. Therefore, genetic investigation should be performed in precision medicine era due to high possibility of hereditary pulmonary arterial hypertension.

Keywords: Hereditary, Pulmonary arterial hypertension, Right heart failure

INTRODUCTION

Despite advancements in therapy during the past 25 years, Pulmonary Arterial Hypertension (PAH)

remains a devastating disease for incident cases with significantly reduced survival.^{1,2} In Germany, the incidence of PAH in 2014 was 3.9 per 1 million adults and the prevalence was 25.9 per 1 million adults.^{3,4} Data from National Cardiovascular Center Harapan Kita (NCCHK), Indonesia in 2017 showed that around 70% patient aged >18 years diagnosed as pulmonary hypertension and majority of those patients (66%) were female and 482 patients were diagnosed having PAH. PAH is a devastating disease of the pulmonary vasculature that is pathologically characterized by progressive neointimal proliferation, smooth muscle cell hypertrophy, and surrounding adventitial expansion leading to occlusive vascular lesions of the smallest pulmonary arteries. Group 1 PAH is divided into disease subgroups that include heritable (HPAH, formerly familial PAH), idiopathic (IPAH), and PAH associated with a variety of other systemic diseases or drug/toxin exposures.⁵ Several studies have reported mutations in the bone morphogenetic protein receptor, type II gene (BMPR2) as causal for PAH in patients with FPAH and IPAH.⁶ Therefore, the aim of this study is to present a rare available data and future perspectives on employing an in-depth analysis of diagnostic cascade to allow an earlier and more reliable diagnosis of possible Hereditary Pulmonary Arterial Hypertension (HPAH).

CASE ILLUSTRATION

Case I

Mr. DE, 44 years old came with complain of worsened fatigue when doing mild exertion like walking in a short distance (less than 100 m) since 1 year ago. Patient had episode of right upper abdominal pain with exercise or bending discomfort while leaning forward that accompanied with abdominal fullness or bloating. His daughter died at 4 years old due to pulmonary hypertension. Vital sign was within normal limit. Peripheral oxygen saturation was 98% and no cyanosis either on lips or tongue. The JVP was distended with accentuated second heart sound (pulmonic-component) and grade 3/6 pan-systolic murmur at left lower sternal border (LLSB) from cardiac auscultation. Liver was enlarged and bilateral leg edema found. Electrocardiography showed sinus rhythm with heart rate 85 bpm, Right Axis Deviation, Right Atrial Enlargement (P wave amplitude > 2.5 mm in the inferior lead and P wave amplitude > 1.5 mm in V1 and V2) Right Ventricular Hypertrophy (RVH) with Right Ventricular (RV) Strain (Figure 1). Lab exam showed elevated NT-pro BNP level (2380 pg/mL), and there was slightly hypokalemia (potassium 3,4 mmol/L). Chest X-ray revealed cardiomegaly, elongated aortic segment, increase pulmonary vascular marking with increased PA segment, convex/ bulging main pulmonary segment, right heart border enlargement = 44,1 mm (>44 mm) from midline to the prominent right heart border, flatten cardiac waist, and upward apex (Figure 2).

Echocardiographic finding was RV and RA dilatation, Reduced right ventricular contractility with TAPSE of 10 mm and normal LV systolic function, global normokinetics, mild tricuspid regurgitation with TRV max= 4,32m/s (>3,0 m/s) and TVR Vmax PG 75 mmHg, early diastolic pulmonary regurgitation >2,2 m/s, enlarged right atrial area (end systole) = 44,5 cm² (> 18 cm²), enlarged pulmonary artery diameter 44 mm (>25 mm), RVOT AccT 79 ms (<105 ms), IVC>21 mm with inspiratory collapse >50% with sniff or >20% with quiet inspiration, RV dominant with RV/LV basal diameter ratio>1, LV eccentricity index >1,1 (Figure 3). RHC showed low flow high pulmonary vascular resistance with non-reactive to oxygen test. Coronary angiography showed normal.

Case II

A 17 years old boy was referred to hospital due to tightness or heavy pressure in left chest with unknown

point of location accompanied by vomiting and cold sweating. Chest pain was felt progressively and the intensity was not reduced by rest. She also had episode of right upper abdominal pain with exercise or bending discomfort while leaning forward that accompanied with abdominal fullness or bloating. His father had similar symptoms and diagnosed having primary pulmonary hypertension. His sister already died at 4 years old due to pulmonary hypertension. Vital sign was within normal limit. Peripheral oxygen saturation was around 96% and there is no cyanosis on lips or tongue. JVP was normal with accentuated second heart sound (pulmonic-component) and grade 2/6 pan-systolic murmur at left lower sternal border (LLSB) from cardiac auscultation. Others physical finding was normal. Electrocardiography showed sinus rhythm with heart rate 88 bpm, Right Axis Deviation, Right Atrial Enlargement (P wave amplitude > 2.5 mm in the inferior lead and P wave amplitude > 1.5 mm in V1 and V2) Right Ventricular Hypertrophy (RVH) with Right Ventricular (RV) Strain (Figure 4). Previous laboratory examination showed elevated serial Troponin-T in 3 hours (Δ Troponin T = 752 pg/mL) with normal D-dimer value (195 ug/mL). However, it found elevated serial d-dimer level (1353 pg/ml) and elevated NT-proBNP level (2393 pg/ml). Previous calcium score showed no significant calcified plaque. CT coronary showed normal coronary and CT angio-pulmonal showed dilated pulmonary artery with dilated right ventricle compatible to pulmonary hypertension (pulmonary artery diameter 30 mm, PA/aorta ratio = 1:3 (normal PA/Ao >0,9), RV wall thickness was >4 mm, lumen ration for RV/LV = 3 (normal ratio for RV/LV >1). Chest X-ray revealed cardiomegaly, elongated aortic segment, increased PA segment (Right Descending Pulmonary artery =27 mm (> 16 mm), Left Descending Pulmonary Artery 33 mm (> 18 mm), convex/ bulging main pulmonary segment, right heart border enlargement (>44 mm from midline to the right heart border), flatten cardiac waist, and upward apex (Figure 2, B).

Echocardiographic finding showed RV and RA dilatation, reduced right ventricular contractility with TAPSE of 10 mm and normal LV systolic function (EF 67,5%), global normokinetics, mild tricuspid regurgitation (TR Vmax= 5,3 m/sec, TVR PG 111 mgHg), RV dominant with RV/LV basal diameter ratio =2,5 (>1), LV eccentricity index >1,1 during systole and or diastole, enlarged right atrial area (end systole) =20,1cm² (>18 cm²), IVC>21 mm with inspiratory collapse >50% with sniff or >20% with quiet inspiration, RVOT AccT = 60 ms (<105 ms) and or mid systolic notching, early diastolic pulmonary regurgitation >2,2 m/s with enlarged pulmonary artery diameter =34 mm (>25 mm) (Figure 5). Lung perfusion scan showed segmental perfusion defect at posterior and anterior-superior lobe, lateral lobe, superior lobe of right pulmonary lobes and segmental perfusion defect at apical posterior, anterior-superior lobe, superior lingula at left pulmonary lobes.

DISCUSSION

We had familial cases showed similar symptoms suggestive of right-sided heart failure. A normal- or low-probability V/Q scan effectively excludes chronic thromboembolic pulmonary hypertension (CTEPH) with a sensitivity of 90–100% and specificity of 94–100%; however, many V/Q scans are not diagnostic. While in PAH the V/Q lung scan may be normal, it may also show small peripheral unmatched and non-segmental defects in perfusion. A caveat is that unmatched perfusion defects may also be seen in other pulmonary vascular diseases. While a V/Q scan is still recommended as the screening test, ventilation scans are often replaced with either a recent chest x-ray or high-resolution lung CT scan.^{7,8} Several factors may affect the risk of death associated with PAH, such as rate of disease progression and signs of right heart failure, or syncope, and comorbidities; age, sex, previous history of therapy, and PAH subtype.^{7,8} Both patients were classified into high-risk category (mortality risk >10%).

Familial Primary Pulmonary Hypertension (PPH) has an autosomal dominant mode of inheritance, reduced penetrance, affects more females than males, and exhibits genetic anticipation.⁹ Since its autosomal dominant mode, the disease could be probability inherited about 50% in each generation. Heterozygous mutations in the *BMPR2* gene are found in nearly 70% of families with heritable PPH and in 25% of patients with sporadic disease. The disease is more common in women (female: male ratio of 1.7:1). However, the penetrance of PPH1 is incomplete, only about 10 to 20% of individuals with *BMPR2* mutations develop the disease during their lifetime, suggesting that development of the disorder is triggered by other genetic or environmental factors. In a previous study, linkage analysis was utilized to map the PPH1 gene to chromosome 2q31 - q32 in 2 ethnically distinct families.⁹ The availability of molecular genetic diagnosis has opened up a new field for patient care, including genetic counselling for PAH. Patients with sporadic or familial PAH or Pulmonary Veno-Occlusive Disease or and Pulmonary Capillary Hemangiomas (PVOD/PCH) should be advised about the availability of genetic testing and counselling because of the strong possibility that they carry a disease-causing mutation. Trained professionals should offer counselling and testing to the patient. Genetic counselling and Bone Morphogenetic Protein Receptor Type 2 (*BMPR2*) mutation screening (point mutations and large rearrangements) should be offered by expert referral centers to patients with Idiopathic Pulmonary Arterial Hypertension (IPAH). Further genetics of *ACVRL1* and *ENG* mutations may be performed if *BMPR2* mutations were absent. While other combination of mutations may predispose to the disease, they are relatively rare; uncommon mutations associated with occurrence of familial PAH include *KCNK3* and *CAV1* mutations.^{7,10-12}

CONCLUSION

We describe familial cases of pulmonary hypertension with clinically presenting right-sided heart failure. Diagnostic investigation was performed according to recent guideline to rule out and rule in all the possible cause of pulmonary hypertension. However, the final assessment showed unknown cause of pre-capillary pulmonary hypertension. Therefore, genetic investigation should be performed in precision medicine era due to high possibility of hereditary pulmonary arterial hypertension.

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Figure Legends

Figure 1. ECG of Mr. DE at admission in NCCHK

Figure 2. Posteroanterior chest X-ray of (A) Mr. DW (B) An.S

Figure 3. Echocardiographic finding in Mr.DE (A). Early diastolic pulmonary regurgitation $>2,2$ m/s, (B) Right atrial area (end systole) = $44,5$ cm² (C) Pulmonary artery diameter 44 mm (D) RVOT AccT 79 ms (<105 ms) (E). IVC >21 mm with inspiratory collapse $>50\%$ with sniff or $>20\%$ with quiet inspiration (F). RV dominant with RV/LV basal diameter ratio >1 .

Figure 4. ECG of An.S at NCCHK.

Figure 5. Echocardiographic finding in An.S(A). RV dominant with RV/LV basal diameter ratio = $2,5$ (>1) (B). Right atrial area (end systole) = $20,1$ cm² (C). IVC >21 mm with inspiratory collapse $>50\%$ with sniff or $>20\%$ with quiet inspiration. (D). Pulmonary artery diameter = 34 mm (>25 mm).

Figure 6. Family tree of possible HPAH