Case Report

Familial Primary Pulmonary Hypertension

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Background: Familial primary pulmonary hypertension (PPH) is a rare, fatal, autosomal dominant disease that results in right heart failure from idiopathic obliteration of the pulmonary arteries.

Introduction

Primary pulmonary hypertension (PPH) is a rare but important disease that affects young people, predominantly women, aged between 20 and 30 years. It is characterized by progressive dyspnea, a rapid downhill course, and an invariably fatal outcome [1, 2].

Primary pulmonary hypertension (PPH) is defined clinically by sustained elevation of pulmonary arterial pressure without a demonstrable cause, and is a progressive, often-fatal disease. PPH can be associated with ingestion of appetite suppressants, human immunodeficiency virus infection and certain autoimmune diseases. Indeed, at least 6% of individuals diagnosed with so-called "primary" pulmonary hypertension have a family history of the disorder. Familial PPH segregates as an autosomal dominant trait but with markedly reduced penetrance. Defects within bone morphogenetic protein receptor type II gene (BMPR2), coding for a type II receptor member of the transforming growth factor beta (TGF-beta) family, have been shown to underlie familial PPH. Germline BMPR2 mutations have been detected in at least 60% of the families studied to date. Disease-associated mutations are predicted to interrupt the BMP-mediated signaling pathway predisposing to proliferation of cells within small pulmonary arteries. Several lines of evidence point to the potentia requirement of additional factors, either environmental or genetic, in the pathogenesis of the disease. In addition, a proportion of idiopathic PPH as well as anorexigen-associated PPH turn out to have an inherited basis, as demonstrated by detection of germline BMPR2 mutations. Analysis of other genes encoding TGF-beta receptor proteins, led to the demonstration that PPH in association with hereditary hemorrhagic telangiectasia, an autosomal dominant vascular dysplasia, can involve other TGF-beta receptor subtypes. These observations support the hypothesis that mutations in the TGF-beta superfamily may be a trigger for pulmonary vascular remodeling. Nevertheless, PPH pathobiology remains unclear and genomic approaches may identify additional molecular determinants for this disorder. [1,2 ,3,4,5].

Polycythemia is found in many cases of pulmonary hypertension that are associated with chronic hypoxemia .ECG changes are those of right axis deviation ,right ventricular hypertrophy ,right ventricular strain ,or right atrial enlargement .Transthoracic echocardiography provided a non-invasive assessment of pulmonary artery pressure and a useful means of monitoring the condition .Right heart catheterization is required to determine whether vasodilatation can reduce pulmonary artery pressure and may therefore be of therapeutic value[1,2].

Management

1. Warfarin
2. high dose of calcium channel blockers
3. Epoprostenol "Prostacycline"
4. PDE5 inhibitor or Sildenafil
5. Bosentan"oral endothelin Antagonist"
6. heart-lungs transplantation.

The median survival from time of diagnosis is 2-3 years [(2)].

Patients and methods

We reported three of nine young males brothers (8males and one female) had sever pulmonary hypertension of unexplained cause .Their parents were non-consanguineous. They were studied subsequently in four years duration. Each patient interview carefully in Al-Hussain Hospital-Karbala, when the diagnosis suspected, patients were referred to the specialized center (Iben Al-Betar hospital for cardiac surgery)in Baghdad – Iraq.Full investigations were done for the patients include ,CBP, Blood Biochemistry, Connective tissue screen, chest X-ray, pulmonary function tests and cardiac catheterization.

When diagnosis settled, patients treated with warfarin, calcium channel blocker, and in advanced stage diuretic, digoxin and oxygen used.

Case (1): Young male -24 years old. The patient was the seventh brother in the family, athletes-football player. The patient developed gradually progressive dyspnea during training, within two months he became a director of the team due to dyspnea. During examination he had fixed splitting S2.Echocardiography showed dilated right atrium and ventricle. The patient was referred to the specialized center for cardiac catheterization where the diagnosis of primary pulmonary hypertension confirmed.

The patient was deteriorated within short time after catheterization, developed advance heart failure and died after 4 months so his brothers refused catheterization when suggested for them.

The time from first examination to death was 9 months.

Case (2) & (3): The fifth and sixth brother in the family, male, their ages at diagnosis were 28 years and 27years respectively.

The patients developed exertional dyspnea after the death of the first case diagnosed as psychological upset, but Echocardiography showed right ventricular hypertrophy .Full investigation was done for both patients as in first case, but the patients refused the catheterization.

The middle one was incompliance with the treatment and died within one year after the diagnosis. The third patient still a live with exertional dyspnea and compliance with treatment, warferin and daltiazim

The three patients were healthy and develop slowly progressive dyspnea. No significant past neither medical, surgical nor drugs history. There is no family history of same presentation.

All patients had polycythemia, normal platelets and WBC counts, Blood biochemistry normal .Liver function tests were normal .Connective tissue diseases screen were negative in the three patients.

The three patients treated with anticoagulant-Warferin and calcium channel blocker – Daltiazim, but unfortunately the first two were incompliance. The last one now stable on treatment. The last patient restricts his activity, avoid heavy duty and upstairs.

Table :(1) Blood tests

Patients	PCV	WBC	Plat.	ANA	LFT	CXR at time of diagnosis
1st	56	6800	N	Neg.	N	N
2nd	50	7200	N	Neg.	N	N
3rd	53	5700	N	Neg.	N	N

N= Normal Neg. Negative

Table :(2) Important points in the history

Patients	Past medical history	Drugs history	Onset of symptoms	Age at diagnosis	Time from diagnosis to the death	Compliance with the treatment
1st	Neg.	Neg.	Gradually	24 years	9 months	Non-compliance
2nd	Neg.	Neg.	Gradually	28 years	One year	Non-compliance
3rd	Neg.	Neg.	Gradually	27 years	Still a live	compliance

Neg. =Negative

Discussion

Primary pulmonary hypertension is a rare disease affecting mostly females. The occurrence of overtly manifest primary pulmonary hypertension is rare in males, especially at an early age [6].

We report a family where 3 of the 9 (8 males and one female) brothers had severe pulmonary hypertension of unexplained cause. All patients were young males, this consistent with Shanmugasundaram S., who report a family where 2 of the 3 male children born to consanguineous parents had severe pulmonary hypertension of unexplained cause [6].

Yamashita K et al studied two cases of familial primary pulmonary hypertension; Case 1, a 28-yea r- old woman (third daughter of Case 2). She died of a pulmonary hypertensive crisis twenty days after readmission and 9 months after the first admission. Case 2, a 60-year-old woman (mother of Case 1) developed the same symptoms as those in Case 1 short time after the death of case 1[7].The time from diagnosis to the death in our cases consist with that time in case(1)[7] .

Our finding regarding the age of patients and time from diagnosis to the death consistent with Jing ZC et al who studied a family of Han nationality in Zhumadian, Henan Province ,Including female , her brother and her daughter .The three patients in this family coming down with the illness at the ages of 35,23, and13 respectively, suffered from severe pulmonary hypertension .The mother died 1 year after the diagnosis [8].

Conclusions

1. Primary pulmonary hypertension should be suspected in any young patient with unexplained exertional dyspnea .
2. Treatments with anticoagulant and calcium channel blocker may improve survival of patients.
3. Restriction of activity has a role in managements of patients with primary pulmonary hypertension.

Refessrences

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