Unexplained severe pulmonary hypertension in two brothers

H.J. Puolijoki, K.O. Niemelä, L.O. Siitonen

Abstract: Unexplained pulmonary hypertension of nearly simultaneous onset is reported in two brothers, aged 17 and 26 yrs. Echocardiography revealed right ventricular hypertrophy and dilatation, paradoxical septal motion and an enlarged main pulmonary artery. In the right catheterization highly elevated pulmonary arterial pressures (107/ 88 and 84/46 mmHg) were seen. Doppler echocardiography showed significant leakage of the pulmonary and tricuspid valves in the younger brother, who died suddenly three weeks later. An initial decline in pulmonary arterial systolic pressure was achieved in the older brother by digital therapy. Eight months later, however, the pressure had risen to the pretreatment level. Dyspnoea increased and the patient underwent heart-lung transplantation but subsequently died. In the family study a mild brother, father and mother were healthy.

Case reports

Case 1

A previously healthy schoolboy, aged 17 yrs, had experienced dyspnoea on exercise since September 1986. Until then he had a normal physical exercise capacity. He was a nonsmoker and used no drugs. On physical examination, he had central cyanosis, his blood pressure was 125/95 mmHg and heart rate was 100 beats·min⁻¹. Cardiac auscultation revealed an accentuated pulmonary heart sound and an ejection sound. There were also systolic and diastolic murmurs suggestive of tricuspid and pulmonary valve insufficiency, respectively. The ECG revealed right ventricular hypertrophy (RVH) and P-pulmonale. On chest X-ray the central pulmonary arteries were thick (fig. 1a), but lung perfusion scintigraphy was normal. The arterial oxygen tension (Pao₂) was only 6.7 kPa (50 mmHg) in spite of hyperventilation with an arterial carbon dioxide tension (Paco₂) of 2.9 kPa (22 mmHg).

Table 1. – Previously published families with primary pulmonary hypertension; number of cases and generations in which disease was found.

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Total 23 46 69

Additional cases of families 2–6 reported by Lovo et al. [1] are included. Families 7–10 were successfully contacted by Lovo et al. but had no new cases. Sex distribution in family is partly unclear.
Doppler echocardiography showed significant regurgitation of the pulmonary and tricuspid valves. On right-heart catheterization the pulmonary artery pressure was 107/58 mmHg, whereas no signs of intracardiac shunting were found. After 10 min of oxygen therapy, the mixed venous oxygen saturation increased from 45 to 75%, and the pulmonary arterial pressure decreased to 97/58 mmHg. The spirometric values were normal whereas the carbon monoxide diffusion capacity (Dco) was markedly reduced, being only 23% of predicted.

Nifedipine therapy, with continuous nasal oxygen, with a flow of 4 l/min was started. In January 1987, less than 3 wks after the diagnosis of unexplained pulmonary hypertension, the patient died suddenly, probably due to a malignant arrhythmia.

At autopsy the diagnosis was verified. No cardiac or large vessel anomalies were found. The diameter of the main pulmonary artery (30 mm) was greater than that of the aorta, and the pulmonary arteries were thick. Microscopic examination showed muscular hypertrophy, plexiform lesions and intimal hyperplasia typical of primary pulmonary hypertension.

Case 2

A fur-worker, aged 26 yrs, brother of case 1, was in good health until November 1986, when he had progressive exertional dyspnœa. Previously he had been an active soccer player. After his brother's death he was admitted to the hospital. He too was a non-smoker and used no drugs. A mild central cyanosis was noticed. His blood pressure was 112/62 mmHg and heart rate 68 beats/min. On cardiac auscultation an accentuated P, but no cardiac murmurs were noticed. The ECG was suggestive of RVH. On chest X-ray the central pulmonary arteries were thick (fig. 1b). The radiocardiography and lung perfusion scintigrams were normal. The echocardiography (fig. 2) showed right ventricular dilatation (with a dimension of 29 mm) and hypertrophy, and the movement of the interventricular septum was paradoxical. No significant pulmonary or tricuspid valve leakage was noticed. The Pao, was 9.6 kPa (72 mmHg), Paco, 2.8 kPa (21 mmHg) and oxygen saturation 97%. No circulating anticoagulants were found, and antithrombin III and protein C values were within normal limits.

On right heart catheterization the pulmonary artery pressure was 84/46 mmHg. The oxygen saturation values revealed no intracardiac shunting. The spirometric values were normal, whilst Dco was only 17% of predicted.

Anticoagulant therapy was started. Calcium antagonist infusion (nimodipine) reduced the pulmonary artery pressure to 63/35 mmHg. Peroral nifedipine together with captopril was therefore started. With this medication the patient's pulmonary artery pressure initially decreased to 58/22 mmHg whilst in bed and 33/19 mmHg whilst standing. After four weeks, however, the pulmonary artery pressure had risen to 70/35 mmHg, whereas the patient was relatively symptom-free.
Eight months later the pulmonary artery pressure was equal to the initial values. The patient's clinical condition deteriorated; $P_{aO_2}$ was about 6.7 kPa (50 mmHg) and, due to progressive dyspnoea and heart failure, he was restricted to bed with continuous oxygen therapy. Heart-lung transplantation was performed but he died nine days later due to pneumonia.

Pathological examination revealed marked right ventricular hypertrophy with thick, enlarged and atheromatous pulmonary arteries without any marks of pulmonary embolization or primary cardiac disease (Fig. 3). The final diagnosis was primary pulmonary hypertension.

**Family study**

A farmer, aged 23 yrs, the brother of cases 1 and 2, had no symptoms. His clinical examination showed no cardiac abnormalities. On the ECG there was a partial right bundle branch block (RBBB). His chest X-ray was normal. On echocardiography the dimensions of the right ventricle and the main pulmonary artery were within normal limits. No significant valvular leakage was observed. His spirometric values, $Dl_{C0}$, and arterial blood saturation were within normal limits.

A farmer, aged 53 yrs, the father of the family, was also symptom-free. His clinical examination, ECG and chest X-ray revealed no cardiac abnormalities. The right ventricular diastolic dimension on echocardiography was 21 mm. The spirometric values and $Dl_{C0}$ were normal, whereas $P_{aO_2}$ was below normal (62 mmHg). He was, however, a smoker.

The mother of the family, aged 47 yrs, was also symptom-free. Her clinical examination showed no cardiac abnormalities. Her chest X-ray was normal. The ECG revealed a partial RBBB but the echocardiography showed no signs of right heart dilatation or other cardiac abnormalities. Her spirometric, $Dl_{C0}$, and $P_{aO_2}$ values were within normal limits.

The family history revealed no previous illness suggestive of unexplained pulmonary hypertension.

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**Discussion**

The most important causes of secondary pulmonary hypertension are chronic lung diseases causing hypoxaemia and repeated stretching of the pulmonary vessels [24]. Cardiac anomalies, valve diseases, shunts, and conditions inducing hypoxaemia like sleep apnoea, may increase pulmonary blood pressure. Chronic pulmonary embolism, causing hypoxaemia, and impedance to flow through pulmonary arteries, leads also to pulmonary hypertension [25]. Primary pulmonary hypertension is a term referring to persistent elevation of pulmonary artery pressure without demonstrable cause.

As in our two cases, the first and predominant symptom of primary pulmonary hypertension is dyspnoea on exercise, which becomes manifest at an advanced stage of the disease [1]. Although the disorder has been
accepted as a clinical entity, the nomenclature is probably non-homogeneous [26]. In the family study the disease was observed in two out of three brothers. Prior to adolescence the incidence of unexplained pulmonary hypertension is said to be equal for males and females, being thereafter predominant in females by a ratio of 10:1 [1, 27]. Although the female to male ratio appears to be 2:1 in the familial cases, a familial disease affecting only males is uncommon (Table 1). Contrary to our family study, most of the familial cases of the disease have been reported in more than one generation (Table 1).

No apparent cause could be found to explain the relatively simultaneous onset of the disease in the brothers. Neither drugs nor chemicals were suspected to cause these cases. Their clinical, echocardiographic and autopsy findings were typical for primary pulmonary hypertension. As the typical findings of pulmonary hypertension such as right ventricular dilatation and hypertrophy, paradoxical septal motion and the leakage of the pulmonary and tricuspid valves are easy to detect on echocardiography [27, 28], its more widespread use helps in making an earlier diagnosis. Semiquantitative measurement of pulmonary artery pressure is possible when using these indicators [27, 28]. As the conventional and the Doppler echocardiography showed no significant cardiac abnormalities in the family study, right heart catheterization was considered unnecessary.

It is not clear whether an earlier diagnosis of unexplained pulmonary hypertension with subsequent treatment results in an improved survival. Most therapeutic trials so far have been disappointing [26]. The use of a high-dose calcium channel blocking agent has resulted in a maintained haemodynamic benefit in some patients [29]. Some encouraging results with vasodilator treatment have also been reported [26, 30-32] although the therapy, as noted in our cases, has not generally provided a substantial decline in pulmonary arterial pressure in the long run (for more than one year). The use of prostacyclin may help to detect those cases responding to vasodilator treatment [33, 34], making perhaps tedious therapeutic trial unnecessary. Although heart-lung transplantation is difficult and complicated, there is no alternative therapy for patients with end-stage pulmonary hypertension. Since 1981 at least 255 patients have undergone this operation for a variety of indications, predominantly primary pulmonary hypertension or congenital heart disease [35].

The rare familial occurrence of primary pulmonary hypertension should be kept in mind. As the echocardiography provides non-invasive means to exclude pulmonary hypertension, all the family members should be examined in cases of unexplained pulmonary hypertension.

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References

UNEXPLAINED PULMONARY HYPERTENSION

353


RÉSUMÉ: Observation d'une hypertension pulmonaire inexplicable d'apparition quasi simultanée chez deux frères, âgés respectivement de 17 et 26 ans. L'échocardiographie met en évidence une hypertrophie et une dilation ventriculaires droites, une motilité septale paradoxale, et un élargissement du tronc de l'artère pulmonaire. Au cathétérisme cardiaque droit, l'on observe une augmentation marquée de la pression artérielle pulmonaire (107/84 & 84/46 mm Hg). Une insuffisance significative des valves pulmonaire et tricuspide est démontrée par l'échocardiographie Doppler chez le frère cadet, qui décède brutalement après trois semaines. Un traitement médicamenteux provoque une diminution transitoire de la pression artérielle pulmonaire systémique chez l'aîné. Toutefois, 8 mois plus tard, la pression rejoint le niveau initial. La dyspnée augmentant, le patient est tourné à une transplantation cardiopulmonaire, suivie d'une issue fatale. Au cours de l'étude de la famille, père, mère et troisième frère s'avèrent bien portants.