Epidemiology and risk factors of pulmonary hypertension

Summary / Zusammenfassung

Our interest in pulmonary hypertension (PH) started 1990. In a retrospective study we analyzed the clinical characteristics, risks and prognostic factors of all patients with idiopathic pulmonary arterial hypertension (IPAH) observed at Zurich University Hospital between 1980 and 1990. In summary, our findings were congruent with those of the NIH registry. We calculated an incidence of the disease in our region (north-east Switzerland) of 1.5 cases per million per year. At that time lung transplantation was the only therapeutic option, and no medical treatments were available. The mean survival of this devastating disease was 2 years. Prognosis was closely correlated with the severity of hemodynamic parameters. All patients with a pulmonary vascular resistance >1000 dyn/sec/sec-5 died within 6 years.

We then initiated the Swiss Registry in 1999. We could trace a total of 106 patients. The diagnosis was IPAH in 37%, PAH associated with known risk factors or diseases in 48%, and chronic thromboembolic pulmonary hypertension (CTEPH) in 15%. At that time, the only available medical therapy consisted of calcium channel blockers (18% of all cases), which however were not very effective. A decade later it could be shown that only 5-10% of IPAH patients actually responded to these drugs. Continuous intravenous prostacyclin (epoprostenol) as the first effective therapy for PAH became available in Switzerland in 2000. Because of various reasons, this approach was used in single patients only. Thus, the Registry revealed that there was no relevant improvement in prognosis, ie. 26% of the patients had died, and 7% had needed lung transplantation.

Fortunately, we could take part in the first large randomized trial in PH, the inhalation of the stable prostacyclin analogue iloprost. Due to our backlog with respect to treatments of PH we were able to include a significant number of patients in this trial. As a consequence, one third of the Swiss Registry patients were receiving this treatment.

The next analysis of the Swiss Registry data on 222 patients was performed in 2004. By then, almost 90% of the 75 IPAH cases were on the new specific treatments, ie. inhaled iloprost, oral bosentan and sildenafil. During the course of their disease almost 70% had a combination therapy. Fortunately, prognosis of these dismal disorders had improved. As for IPAH, the 1- and 3-year survival had increased from 67% and 46% to 89% and 73%, respectively.

As for potential risk factors and/or diseases for the development of PAH, besides the HIV-associated PAH, we were one of the first groups to describe the increased incidence of PH in patients with hyperthyroidism. The medical records of 45 patients were used retrospectively to identify patients with hyperthyroidism and pulmonary hypertension over a three-year period (April 1993 to April 1996). Systolic pulmonary artery pressure (sPAP) was determined by continuous-wave Doppler echocardiography according to standard techniques.

We identified 4 patients with PH showing elevated sPAP of 40±11 mmHg. After successful therapy of hyperthyroidism the sPAP decreased in all patients to a mean of 25±6 mmHg. We concluded that the observation of four patients with PH and hyperthyroidism is striking and suggests a possible pathogenic link of these disorders. Interestingly, this paper is cited more than 40 times by now, corroborating our suspicion of the association of hyperthyroidism with PH. As a consequence, at the recent WHO symposium hyperthyroidism was included into group 5 of disorders multi-factorially associated with PH.

Later, in a case-control study we provided first evidence that subcutaneous arteriolosclerosis, the hallmark of Martorell ulcer, is associated with PH. In patients with Martorell sPAP was
significantly higher than in the control group (34±17 vs 25±7 mmHg (P = 0.023). The prevalence of PH was 31% (5/14) in patients and 7% (2/28) in controls (p = 0.031). Hence, we provided the first evidence that Martorell ulcer is associated with PH.

Furthermore, our group identified three other very rare conditions associated with PH. Firstly, we described an unusual course in a patient with known perinatal pulmonary complications due to a Pierre Robin anomaly. PH was diagnosed at the age of 18 months. This patient in fact suffering from a rare complication of this very rare disease died after an unusual long course from progressive right heart failure at the age of 19 years.

Subsequently, we described a patient with Klippel-Trenaunay syndrome and PH. Chronic thromboembolic PH could be excluded. Hence, we hypothesized that Klippel-Trenaunay syndrome is another disease associated with PAH, possibly due to haemodynamic changes of small vessel abnormalities.

In addition, we described 2 patients with multiple peripheral pulmonary artery stenoses presenting with severe PH in adulthood, a constellation which has only once been described previously. Both patients lived without significant health problems for decades. However, after onset of symptoms, their medical condition declined rapidly despite vasodilator therapy, necessitating lung transplantation several months after the diagnosis.

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