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Pulmonary veno-occlusive disease: characterising a rare but important disease

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Although there is no standardised definition of an ultra-rare disease, pulmonary veno-occlusive disease (PVOD) would certainly qualify. The condition has a prevalence of less than 1 per million of the population, and yet most physicians are familiar with the term. PVOD is classified as a rare form of pulmonary arterial hypertension (PAH) (1). The disease usually manifests in younger adults and is considered to carry a particularly poor prognosis compared with other forms of PAH. Amongst pulmonary hypertension specialists it is an unwelcome diagnosis since it has a reputation for responding poorly to available PAH therapies, and indeed these therapies may precipitate fatal pulmonary oedema (2, 3). Being an ultra-rare condition, PVOD has retained an aura of mystery, but now the paper by Montani et al. in this issue of the *Lancet Respiratory Medicine* provides new insights into the molecular and clinical characterisation of this disease in the largest published cohort to date.

The paper by Montani et al. follows up on the recent discovery of biallelic mutations in the *EIF2AK4* gene as the major genetic cause of PVOD. Recessive mutations in *EIF2AK4* account for nearly 100% of families with PVOD, and approximately 25% of sporadic cases (4). The finding of biallelic *EIF2AK4* mutations in cases of pulmonary capillary haemangiomatosis (PCH) also suggests that PVOD and PCH are essentially manifestations of the same disease (5). The present paper describes the clinical course of disease in PVOD/PCH patients with and without biallelic *EIF2AK4* mutations. Mutation carriers had a significantly younger age of diagnosis and subsequently were more likely to be transplanted. However, no survival difference was demonstrated between the two groups. Additionally, lung function and haemodynamic parameters were similar to those with no *EIF2AK4* mutations. As reported in a previous publication by the group, patients without *EIF2AK4* mutations were far more likely to have been exposed to inorganic solvents as well as to have received chemotherapy prior to the development of disease (6).

Thus the genetic and environmental factors involved in the aetiology of PVOD/PCH are becoming clearer. What remains unclear are the mechanisms by which these mutations and indeed the exposure to noxious agents, precipitates disease. It is remarkable that mutations in *EIF2AK4*, a ubiquitously expressed kinase of the cell integrated stress response, typically in response to amino acid deprivation, manifest as this rare lung disease. Pre-clinical models have shown that phenotypic expression of the *EIF2AK4* knockout requires additional environmental stresses such as amino acid starvation (7). Whether such stresses influences disease manifestation in humans with biallelic *EIF2AK4* mutations has not been explored. Much remains to be discovered regarding the mechanisms, and whether this might yield new approaches to treating this devastating disease.

The present report confirms that the clinical response to therapies currently licensed for PAH is very modest in patients with PVOD/PCH. This observation, coupled with a risk of life-threatening pulmonary oedema precipitated by these drugs in over 20% of cases, should prompt the physician to refer for early assessment for lung transplantation. Although overall clinical improvement in response to drug therapy was modest, it might be possible in future studies to stratify PVOD/PCH patients based on risk of pulmonary oedema or genotype.

Finally, the distinction between PVOD and PAH can be subtle. Up to 10% of patients with a clinical diagnosis of idiopathic PAH may have evidence for PVOD. Clinical characteristics such as a low transfer coefficient for carbon monoxide have also been described in a subset of patients with PAH, as have radiological features such centrilobular ground-glass opacification (8). The gold standard for diagnosis of PVOD/PCH is histological assessment. However, since lung biopsy is contraindicated in PAH such confirmation usually occurs only following death or transplantation. The finding of bilallelic mutations in *EIF2AK4* might now be used to confirm a suspected diagnosis, but confounding this there have been reports of families with biallelic mutations in *EIF2AK4* where the diagnosis was thought to be PAH (9, 10). We believe these reports are more likely to be examples of mis-classification of PAH, although analysis of *EIF2AK4* mutations in larger cohorts of PAH patients will be required to confirm this. The finding of an isolated markedly reduced diffusion capacity for carbon monoxide is a consistent feature of such patients, which strongly suggests underlying PVOD/PCH.

The paper by Montani et al provides a definitive description of PVOD/PCH and the impact of *EIF2AK4* mutations. This series, all enrolled in the French Pulmonary Hypertension Registry, is the largest to date. However, even larger international collaborations will be required to have sufficient power to identify and explain the heterogeneity in phenotypes observed and provide further clues to the mechanisms by which these arise.

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