Genetic counselling for pulmonary arterial hypertension: a matter of variable variability

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Abstract We report three cases which highlight the complex considerations surrounding genetic counselling for pulmonary arterial hypertension (PAH). The first counselee developed PAH symptoms shortly after his daughter's death from PAH and was diagnosed with a delay of 1 year. An early diagnosis of familial PAH was established in the second counselee. Oral therapy was initiated immediately, and her functional status has since remained stable. The third counselee was a healthy woman who struggled to cope with her risk for familial PAH, having lost two siblings from the disease. These cases show that incomplete penetrance and variable expression need particular attention during clinical assessment and genetic counselling of heritable PAH patients and family members.

Keywords Heritable pulmonary arterial hypertension · *BMPR2* gene · Genetic counselling · Incomplete penetrance · Variable expression

Introduction

Pulmonary arterial hypertension (PAH) is a devastating disorder characterised by increased pulmonary vascular resistance, ultimately leading to right heart failure and premature death [1]. Recent evidence from a French

registry suggests that the prevalence of PAH is about 15 per million [2]. Despite major advances in the understanding of the pathogenesis of PAH, none of the current therapeutic approaches achieves a cure for this disorder [3].

Different subtypes of PAH have been recognised such as idiopathic PAH (IPAH), heritable PAH (HPAH) and forms associated with various disorders. IPAH corresponds to sporadic disease in which there is neither a family history of PAH nor an identified associated disorder. HPAH includes IPAH cases with germline mutations and familial cases with or without identified germline mutations [4]. HPAH is mainly related to mutations in the bone morphogenetic protein (BMP) type II receptor gene (*BMPR2*), a member of the transforming growth factor β signalling family [5, 6]. Mutations in the *BMPR2* gene have been identified in >70% of familial PAH and in approximately 20% of IPAH cases [5–8]. *BMPR2*-related HPAH is an autosomal dominant disorder which exhibits both incomplete penetrance (the percentage of individuals who have inherited a germline mutation in the same gene expressing the corresponding disorder to any degree is <100%) and variable expression (variation in the severity of the disorder in individuals who have inherited a germline mutation in the same gene) [9]. Disease penetrance in case of a *BMPR2* mutation ranges from 15% to 80% [10]. The variable expression is reflected by for instance inter- and intra-familial differences in age at disease onset and natural history.

Genetic counselling is increasingly part of clinical practise. Symptomatic and predictive (presymptomatic) genetic testing is performed for a wide range of heritable disorders characterised by different levels of penetrance and/or expression. Incomplete penetrance and variable expression need particular attention during clinical assess-

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ment and genetic counselling of HPAH patients and family members. This is demonstrated by the three case reports described below which highlight the complex considerations surrounding genetic counselling for PAH.

Case Reports

Counselee A (Fig. 1a) is a man whose daughter had been diagnosed with PAH at the age of 9 years. No underlying cause was identified. In spite of treatment, disease severity gradually worsened. She died of PAH at the age of 12. Shortly after her death, counselee A himself developed symptoms of fatigue and dyspnoea on exertion. He consulted his family doctor who deemed it unlikely that his symptoms could be attributed to PAH. Instead, the symptoms were attributed to the coping process following his daughter's death. Eventually, after about 1 year, counselee A was referred to our hospital where he was diagnosed with PAH at the age of 39. No underlying cause was identified. He was subsequently referred to the genetic outpatient clinic. Symptomatic genetic testing of the *BMPR2* gene revealed a putative pathogenic germline *BMPR2* mutation. The same mutation was found in stored DNA of his deceased daughter. Nearly 2 years after

counselee A had been diagnosed, he died at the age of 41 due to PAH.

Counselee B is a young healthy woman whose mother was diagnosed with PAH at the age of 45 after several years of progressive complaints of fatigue and dyspnoea. A maternal cousin of her mother had died of PAH (Fig. 1b). No underlying cause had been identified, and no genetic testing of the *BMPR2* gene had been performed in the family. Following genetic counselling, a pathogenic mutation in the *BMPR2* gene was identified in the mother of counselee B. Subsequently, both counselee B and her healthy brother were referred to our genetic outpatient clinic to discuss predictive testing. For both, the most important reason for genetic testing was to learn about their future children's risk. Only counselee B was shown to have inherited the familial *BMPR2* mutation. Periodic pulmonary and cardiological screenings were initiated. Before her first pregnancy, she was examined thoroughly and no signs of PAH were identified. Shortly after an uncomplicated pregnancy and delivery, counselee B developed progressive complaints of fatigue. Echocardiography showed increased pressures in the pulmonary artery. At the age of 27, PAH was confirmed by right heart catheterisation. With oral medication, her functional status has since remained stable for several years in New York Heart Association class II.

Case C (Fig. 1c) relates to a healthy couple with two daughters and one son. Two of their children had died of PAH at 19 and 11 years of age, respectively. Before her death, a pathogenic mutation in the *BMPR2* gene was identified in the daughter. On the basis of this result, the conclusion seemed warranted that their son had also inherited the same *BMPR2* mutation. Therefore, the mutation was either of paternal or maternal origin even though both family branches did not include additional cases of PAH. Predictive genetic testing was discussed with the couple. Because of the medical history of their daughter and son, genetic predisposition for PAH to them was synonymous to developing PAH with a poor prognosis. For this reason, they chose not to perform predictive genetic testing. Shortly afterwards, their daughter approached our clinic to discuss predictive genetic testing. The potential advantage of screening was her most important reason for genetic testing. She indicated that she would not discuss a positive genetic test outcome with her parents because they would interpret this as a poor prognosis for their only living child. Following time for reflection, she decided to proceed with predictive genetic testing. She was shown to have inherited the familial *BMPR2* mutation. Afterwards, she had additional discussions with the genetic nurse and pulmonologist about coping difficulties with regard to the positive genetic test outcome. There has been no contact with her since then.

Fig. 1 Pedigrees of counselee A, B and C. White square healthy man; white circle healthy woman; black square and black circle man and woman, respectively, diagnosed with heritable pulmonary arterial hypertension; arrow counselee, solidus deceased)

Discussion

Genetic counselling for PAH should be considered when no underlying cause has been identified. It entails family studies, discussion of the medical and genetic aspects of the disorder and of genetic testing. A specialised social worker or psychologist can support the decision and coping process with regard to genetic testing for patients and healthy family members. A genetic test result can be of great value. When a *BMPR2* mutation is identified, genetic predisposition is confirmed and predictive testing in family members is possible. Relatives who test negative can be reassured. On the other hand, healthy relatives who test positive are at increased risk for developing PAH. They are informed about the possible symptoms. Furthermore, periodic screening aimed at early diagnosis and treatment is warranted in such individuals.

Data about the reasons for genetic testing in PAH are scarcely available. The possible benefit of the outcome for their children and/or other family members seems the most important consideration for patients [11, 12]. No data are available about the psychosocial aspects of genetic testing for PAH.

In case of a positive family history, genetic predisposition is certain even if it is not confirmed by a positive genetic test outcome, i.e. a pathogenic *BMPR2* mutation. This is because it is highly unlikely that a relatively rare disease such as PAH spontaneously affects two or more close relatives. Also, in case of a negative family history, genetic predisposition is not excluded by a negative test outcome. This is because it is not certain that all *BMPR2* mutations are identified by current techniques. Moreover, it is possible that HPAH is caused by mutations in another (yet unknown) gene.

A positive genetic test result currently does not have consequences for the PAH patient. Recent reports have related *BMPR2* mutation status to specific clinical characteristics. It is therefore anticipated that this status will have therapeutic consequences in the near future [12, 13].

The incomplete penetrance and variable expression of *BMPR2*-related HPAH may complicate considerations surrounding genetic counselling. Although HPAH can occur ‘de novo’, the low mean penetrance may obscure a positive family history because the occurrence of disease has skipped one or more generations. Moreover, the low mean penetrance for a healthy individual who has inherited a *BMPR2* mutation should be weighed against the potential negative consequences of such a positive genetic test outcome for insurance and employment [14]. For healthy family members of HPAH patients, it may be sufficient to provide information about the symptoms of PAH. The symptoms, however, are nonspecific which may nevertheless delay the diagnostic process [2, 15]. This is illustrated by case A in which earlier knowledge about a potential role

of genetic predisposition in the family would likely have resulted in earlier consideration of PAH as an explanation for counsellee A’s complaints. An early diagnosis on the other hand was established in counsellee B and treatment was initiated immediately. Her functional status has since remained stable. Whether early treatment in general leads to a better prognosis to date is uncertain.

Intrafamilial variability is illustrated by all discussed cases. The variability in age at disease onset is most prominently illustrated by case A. For patients and family members, this variability is difficult to comprehend. They seem to attach value to the clinical manifestation in the first diagnosed patient in the family, the patient with the least serious manifestation of disease and/or the closest family member.

The discussed cases demonstrate that incomplete penetrance and variable expression need particular attention during clinical assessment and genetic counselling of HPAH patients and family members. Furthermore, it may be preferable to offer the clinical genetic services in specialised PAH centres.

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