Clinical report

Pulmonary arterial hypertension and portal hypertension in a patient with hereditary hemorrhagic telangiectasia

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ABSTRACT

Background and objective: Pulmonary arterial hypertension (PAH) is a rare disease that could be inherited with an autosomal dominant pattern. Mutations in BMPR2 gene are described in over 70% of cases, although other genes are involved in lesser extend in PAH. Hereditary hemorrhagic telangiectasia (HHT) is another rare autosomal dominant disease. PAH is a rare complication of HHT that occurs in less than 1% of cases. Liver cirrhosis with portal hypertension is also associated with the presence of PAHs in 1–2% of cases.

Patients: We present here a patient with HHT who developed PAH shortly after showing portal hypertension.

Results: Some genes (BMPR2, ACVRL1, ENG) seem to play an important role in PAH pathogenesis. We analyzed these genes, detecting mutations in BMPR2 gene (c.1021G>A (V341L), c.327G>A (p.Q109Q)), ACVRL1 (c.313+20C>A, c.1502+7A→G) and ENG (c.498G>A (Q166Q)). The patient also had 3 polymorphisms in the TRPC6 gene (c.1-361A>T, c.1-254C>G, c.1-218C>T).

Conclusions: The study of these genes will help us to identify and track individuals susceptible for developing PAH associated with other diseases.

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Hipertensión arterial pulmonar e hipertensión portal en un paciente con telangiectasia hemorrágica hereditaria

RESUMEN

Fundamento y objetivo: La hipertensión arterial pulmonar (HAP) es una enfermedad rara que en la forma hereditaria se expresa como una afección autosómica dominante. Las mutaciones en el gen BMPR2 son características en más del 70% de los casos, y otros genes están envueltos en la compleja patogénesis de la HAP. La telangiectasia hemorrágica hereditaria (THH) es otra enfermedad rara autosómica dominante. La HAP es una complicación rara de la THH que ocurre en menos del 1% de los casos. La cirrosis hepática con hipertensión portal también se asocia con la presencia de HAP en el 1–2% de los casos.

Pacientes: Presentamos un paciente con THH que desarrolló HAP poco tiempo después de presentar hipertensión portal.

Resultados: Varios genes (BMPR2, ACVRL1, ENG) parecen tener un papel importante en su patogénesis. Se estudiaron a nivel molecular los cambios en estos genes, encontrándose mutaciones en el gen BMPR2 (c.1021G>A (V341L), c.327G>A (p.Q109Q)), ACVRL1 (c.313+20C>A, c.1502+7A→G) y ENG (c.498G>A
Introduction

Pulmonary arterial hypertension (PAH) is a rare disease with a complex pathogenesis that may be heritable, idiopathic or associated with other diseases, drugs or toxins and possibly influenced by genetic factors. Group I of the Nice classification includes idiopathic and hereditary forms and others associated to connective tissue diseases, portal hypertension, HIV infection, schistosomiasis and congenital heart diseases. More than 70% of the hereditary cases are carriers of mutations in the gene that codifies for the Bone morphogenetic protein receptor type 2 (BMPR2). Although familial individuals of a PAH patient with a BMPR2 mutation and carrying the mutation have a risk to develop the disease of around 20%, indicating that more than a single mutation is necessary to develop PAH, perhaps other genetic or exogenous factors play a role. Hereditary hemorrhagic telangiectasia (HHT) is an autosomal dominant disorder with a prevalence of approximately 10 cases per 100,000 inhabitants. HHT is characterized by the presence of epistaxis, mucocutaneous telangiectasias and lung, brain and liver vascular malformations. PAH is a rare complication of HHT, which happens in less than 1% of the cases but implies a marked worsening of prognosis. The genes of Activin receptor like kinase 1 (ACVRL1) and Endoglin (ENG) seem to have an important role in its pathogenesis. Liver cirrhosis with portal hypertension is also associated with the presence of PAH in 1–2% of cases. We present a patient with HHT and liver cirrhosis with portal hypertension that developed PAH. Likely, the interaction between all of these factors favors the appearance of PAH.

Case report

A 62-year-old male was sent to our Unit of PAH because of dyspnea on exertion and suspicion of PAH in an echocardiographic study. He was diagnosed 25 years before of HHT with spontaneous and very frequent nose bleeds, chronic iron deficiency anemia and multiple cutaneous and digestive telangiectasias, including esophagus, stomach and colon, with several episodes of gastrointestinal bleeding. He had no known family history of the disease and only a healthy daughter. In 1981, a secundum atrial septal defect was corrected with no later problems and there were several normal echocardiograms in subsequent reviews. He was a heavy alcohol drinker, and four years before he was detected to have alcohol liver cirrhosis with a single episode of bleeding from one esophageal vein in 2009. In late 2010, a CT (computer tomography) scan showed the presence of portal hypertension without ascites. At that time he was in functional class (FC) I. A year later he began to notice dyspnea on ordinary exertion and subsequently orthopnea and dizziness. He was referred to our Unit 6 months after onset of symptoms, with an echocardiogram that showed marked dilatation of the right cavities, severe tricuspid regurgitation, TAPSE 18 mm and an estimated pulmonary systolic pressure of 80 mmHg. At this time he was in FC III, with Child–Pugh score 87. On physical examination BP was 115/55 mmHg, pulse was 89 beats/min and respiratory rate 17 breaths/min. Pulmonary function tests were normal, and a 6-min walk distance was 275 m, with a resting oxygen saturation on room air of 93% and 74% at the end of the test. The plasma concentration of BNP was 267 pg/ml. A pulmonary V/Q scanning was normal. The CT scan showed large dilated main pulmonary arteries with a diameter of nearly 3 cm (Fig. 1), but no pulmonary vascular malformations. The liver was large with increasing diameter of the hepatic veins and minimal ascites. Cardiac catheterization was performed showing a mean pulmonary arterial pressure of 60 mmHg, systolic pulmonary arterial pressure of 85 mmHg, pulmonary capillary wedge pressure of 14 mmHg, mean right atrial pressure of 12 mmHg, cardiac output of 4.9 L/min, and pulmonary vascular resistance of 871 d/s/cm². The left cavities were normal with no passage of contrast to the right. The vasodilator test with epoprostenol was negative. The patient was treated with ambrisentan 5 mg/d with mild clinical improvement for 2 months but worsened again and the dose was increased to 10 mg/d and tadalafil 40 mg/d was added. After two weeks of treatment without improvement, subcutaneous terpentol was added but the patient had epistaxis and recurrent lower gastrointestinal bleeding in relation to multiple telangiectasias in the colon that drove frequent blood transfusions. He developed severe anemia, progressive renal failure, hyponatremia, generalized edema and finally died three weeks later.

Results

After informed consent, we conducted a genetic study that included BMP2, ACVRL1, ENG and KCNA5 (voltage-gated potassium channel) genes. PolyPhen, Sift and pMUT informatics programs were used to evaluate the potential pathogenicity in the case of missense mutations and NNSplice and NetGene to test their possible involvement in splicing. In BMP2 gene we found a potentially pathogenic missense mutation, c.1021G>A (V341L), and one synonymous mutation, c.327G>A (p.Q109Q), which could affect splicing. In ACVRL1 two changes were present in the intronic region, c.313+20C>A, which seems to have no effect, and c.1502+7A>G which could also affect the splicing. The ENG gene showed a single mutation in exon 4, c.498C>A (Q166Q) with possible involvement in the splicing. No pathogenic mutations were found for KCNA5 gene. The patient also had single nucleotide polymorphisms in the gene, for the Canonical transient receptor potential channels of calcium 6 (TRPC6), c.1-361A>T, c.1-254C>G

![Fig. 1](image-url). In this CT, an increase in the diameter of the pulmonary arteries without vascular malformation was observed.
and c.1-218C>T, which appears to increase the likelihood of developing PAH. The mutations can be show in Fig. 2.

Discussion

This case illustrates the complexity of the pathogenesis of PAH. Although there are other diseases, toxic, drugs or genetic alterations associated with this disease, none by itself seems to be sufficient to develop it. HHT is a relatively common disease, but the presence of PAH occurs in more than 1% of all patients. Portal hypertension also has a high prevalence but the risk of clinically relevant PAH is probably less than 2%. BMPR2 mutations, the most important genetic alteration associated with PAH, lead to occurrence of disease in only 1 out of 5 carriers, possibly indicating that in most of cases it requires the presence of a second hit. Numerous mechanisms are involved in regulation of pulmonary vascular tone and in maintaining a proper endothelial function. It is likely that a pathological change in only one of them can be compensated at least in part and does not have significant consequences, but the coexistence of several damaged cell signals or the occurrence of an external agent may exceed the compensation mechanisms. It has been reported the case of a woman with HHT and gross deletion of ENG gene who developed PAH after years of methamphetamine consumption.\(^5\) Our patient had two PAH-associated diseases and was carrying several mutations in BMPR2, ACVRL1 and ENG, some of them with potential pathogenic effect. Mutations in ACVRL1 usually are associated with an early onset of PAH, often teenagers or children, with an average of 22 years.\(^6\) In our case, the age of onset was clearly superior, but it should be noted that our patient had a mutation whose effects are likely pathogenic. He was also carrying another potential pathogenic mutation in ENG gene, although this gene appears to be less important in the development of PAH. Furthermore, he showed three single nucleotide polymorphisms in TRPC6 gene that increases expression of this receptor leading to an increase of the cellular influx of Ca\(^{2+}\) into the muscle cells of pulmonary arteries in patients with PAH.\(^7\) This polymorphism is almost three times more frequent in these patients than in healthy population. The genetic basis of the PAH has been expanding in recent years. An association between some single-nucleotide polymorphisms of KCNA5 and PAH related to scleroderma have been described.\(^8\)

It is difficult to know to what extent each of the diseases contributed to the development of PAH. There are significant gaps in our knowledge of the molecular mechanisms underlying the disease but we know that the various pathways involved in the pathogenesis of PAH have important relations between them, for example, BMPR2 and ENG,\(^9\) a key player in PAH, or Nitric oxide.\(^10\) Liver cirrhosis was of moderate severity in our case, but there is no clear relationship between severity of portal hypertension and PAH. A case-control study found a significant association with female sex and liver autoimmune diseases,\(^11\) none of which occurred in our case. However, the fact of the appearance of PAH at a relatively late age, a few years after the diagnosis of portal hypertension and a relatively high cardiac output suggests an
important role of liver disease. The presence of HHT associated with some mutations with possible pathogenic potential is another major risk factor in our patient in whom added genetic variants may also favor the development of PAH. Those patients with increased risk of developing PAH should be studied for the presence of genetic variants since the risk could increase significantly.\textsuperscript{12} The poor prognosis, strongly influenced by PAH, was also marked by intractable bleeding due to HHT.

In conclusion, we present a case with PAH in which diverse circumstances may play a role favoring the disease, including genetics. A greater understanding of the genes involved in the development of PAH will help us to better define susceptible individuals, and thereby facilitate advice on avoiding substances or situations that increase the risk of PAH or follow more closely patients with associated diseases.

Conflict of interest

A. Baloira has participated as a consultant for Actelion, GSK, Ferrer and Pfizer and has received research grants from Actelion.

References