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Clinical report

Pulmonary arterial hypertension associated with human immunodeficiency virus infection: study of 4 cases☆

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ABSTRACT

Background and objective: Pulmonary arterial hypertension (PAH) is a rare and progressive disease that can be inherited as autosomal dominant form. The *BMPR2*, *ACVRL1* and *ENG* genes are main genes involved in the pathology. PAH associated to human immunodeficiency virus (HIV) is another rare disease with a low incidence, prevalence and survival. The main objective of this analysis was to study the clinical and molecular characteristics of PAH associated to HIV patients.
Patients: We present 4 cases of HIV patients who developed PAH and have been treated with ambrisentan.
Results: Pathogenic mutations have been identify in analyzed genes in 3 of the four analyzed patients. In addition, these patients present other changes classified as benign after a thorough *in silico* analysis. We identified some changes in genetic modifiers that predispose to these patients to more severe phenotype.
Conclusions: The clinical analysis can help to define monitoring for these patients and the administration of appropriate treatment. These patients also have shown several pathogenic mutations.

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Hipertensión arterial pulmonar asociada a infección por el virus de la inmunodeficiencia humana: análisis de 4 casos

Palabras clave:
Hipertensión arterial pulmonar
Virus de la inmunodeficiencia humana
Ambrisentan
Análisis mutacional

RESUMEN

Fundamentos y objetivos: La hipertensión arterial pulmonar (HAP) es una enfermedad rara y progresiva que se puede heredar de forma autosómica dominante. Los genes *BMPR2*, *ACVRL1* y *ENG* son los principales relacionados con la enfermedad. La HAP asociada al virus de la inmunodeficiencia humana (VIH) es otra enfermedad rara con una incidencia, prevalencia y supervivencia muy bajas. El principal objetivo de este trabajo fue analizar las características clínicas y moleculares de pacientes con HAP asociada al VIH.
Pacientes: Presentamos 4 casos de pacientes con VIH que han desarrollado HAP y han sido tratados con ambrisentan.
Resultados: Se han identificado mutaciones patogénicas en los genes analizados en 3 de los 4 pacientes estudiados. Asimismo, estos pacientes presentan otros cambios clasificados como benignos tras un exhaustivo análisis *in silico*. Tras el análisis de los modificadores genéticos se han identificado cambios que predisponen a los pacientes a padecer un fenotipo más grave.
Conclusiones: El análisis clínico nos ayudará a definir un seguimiento para estos pacientes y a la administración de un tratamiento adecuado. Asimismo, estos pacientes han mostrado un elevado número de mutaciones patogénicas.

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Introduction

Pulmonary arterial hypertension (PAH) (PAH; OMIM # 178600, ORPHA 422) is a rare, progressive disease with reduced incidence and prevalence in the Spanish population, but with poor prognosis in terms of quality of life, morbidity and mortality.[1] Its aetiology is diverse, producing a large variability, both clinically and genetically, and hindering the management of these patients, as well as a systematic diagnostic study.[2,3]

The first case of PAH associated with human immunodeficiency virus (HIV PAH), was described in 1987, with more cases being reported later. Today, HIV-PAH is considered a rare disease whose prevalence is estimated at up to 0.5%.[4] These patients present with plexiform lesions similar to those of other patients with associated PAH.[4–6] Diastolic dysfunction characteristic of HIV patients could contribute to increased intracardiac pressure, exacerbating the PAH phenotype.[5] Viral antigens have been shown to stimulate abnormal pulmonary endothelial cell growth and proliferation, resulting in an increase in apoptotic markers and secretion of endothelin-1, creating an imbalance between apoptosis and proliferation.[5] Since the onset of the first symptoms until patients with HIV-PAH are diagnosed, an average of 6 months elapsed, while in patients with idiopathic PAH, the time involved is an average of 2½ years, approximately.[6] The HIV-PAH patients have a 3-year survival of 84%, which is reduced to 28% in patients with severe PAH.[6] 59% of cases of HIV-PAH patients are using drugs intravenously.[6,7]

As for the genetic basis of PAH, the main gene involved is the *Bone Morphogenetic Protein Receptor type II* (*BMPR2*) located on chromosome 2q33.[8] Since then, more genes have been described, such as *Activin A Receptor Type II-Like 1* (*ACVRL1*) or Endoglin (*ENG*).[8,9] Genetic modifiers that interact with the genes involved in the pathogenesis of PAH have also been associated, modifying the phenotype to produce vasoconstriction and proliferation (*TRPC6*, *AGTR1*, *EDN1*, . . .) or vasodilation (*NOS2*).[10,11]

In this paper we describe the clinical characteristics and genetic alterations of key genes and genetic modifiers of 4 patients with HIV-PAH.

Clinical observation

Three men and 1 woman with a mean age at diagnosis of 44 years (42–47) are included. Hepatitis C virus infection coexisted in 2 patients. The onset of symptoms of PAH occurred after an average of 6 years (3–15) following the first positive serology for HIV. In one case it was a chance discovery when performing an echocardiogram after suspected pulmonary embolism, as the patient did not report dyspnoea. In other cases, the average time elapsed since the patient experienced any symptoms until diagnosis of PAH was 1 month.

Three of the patients had been addicted to intravenous drugs. All were under antiretroviral treatment. Pulmonary embolism was excluded in the 4 cases. Dyspnoea was the main symptom. Two patients were in functional class (FC) II and the other 2 in FC III. The echocardiogram showed severe dilation of right cavities with deviated septum to the left in all cases. The mean pulmonary arterial pressure measured by catheterization was 50 mmHg (35–57), cardiac index 2.43 l/m/m^2 (1.71–3.2), portal blood pressure 11 mmHg (10–12) and pulmonary vascular resistance 780 ds/cm^{-5}/m^2 (400–1120). The vasodilator test was negative in all patients. The average distance covered in the 6-min walk test was 350 m (225–556).

In one patient, treatment was initiated with sildenafil. This had to be withdrawn due to interactions with antiretroviral drugs and was substituted with ambrisentan. Ambrisentan was chosen for the remaining patients, at a dose of 5 mg/d. A favourable response was observed in 3 patients, being necessary to add nebulized iloprost in one of them. After 3, 4 and 6 years of follow up, they continue alive in FC II. The other case responded well initially, staying in FC II for a year but showing progressive worsening of the underlying disease and died from sepsis within 20 months of PAH diagnosis. These results are shown in Table 1.

Genetic study

The study was approved by the Galician Regional Research Ethics Committee, in harmony with the ethical and clinical practices of the Government of Spain and the Declaration of Helsinki. All patients signed an informed consent for genetic testing.

After the genetic analysis of these 4 patients, mutations were detected in genes *BMPR2*, *ACVRL1* and *ENG*. Two of the patients have a pathogenic mutation in the *BMPR2* gene, 2 patients have mutations in the *ENG* gene and only one patient is carrying a pathogenic mutation in the *ACVRL1* gene. Case 1 presented a mutation in *BMPR2* (p.H688Q) and *ENG* (p.R554C) genes, both classified as pathogenic after the *in silico* analysis of the changes. Case 2 showed two pathogenic mutations, one in the *ACVRL1* (P.S232T) gene and another in the *ENG* (P.F474Y) gene. Case 3 presented a pathogenic mutation in the *BMPR2* (P.V341M) gene. Finally, case 4 revealed a mutation in the *ENG* (P.G191N) gene, however, we cannot say whether this mutation is pathogenic, since although the *in silico* analysis classified it as pathogenic other studies classified it as polymorphism (Table 2).

Except the p.R554C of the *ENG* gene, all other detected mutations are preserved throughout evolution, as these are not altered after having compared the wild-type sequence of the altered point with 10 different species, showing a high homology with other species. Therefore, the changes observed are rare variants. On the contrary, the point where the p.R554C mutation is located presents no homologies between different species (Fig. 1).

Regarding the genetic modifiers, 3 of the 4 cases studied show the c.1-1853_1897del44 polymorphism in the *SLC6A4* gene and the

Table 1
Clinical and haemodynamic characteristics in patients with HIV-PAH included in this analysis.

Clinical and haemodynamic characteristics	Patients with PAH associated with HIV			
	Patient 1	Patient 2	Patient 3	Patient 4
Sex	Female	Male	Male	Male
Age at diagnosis (years)	44	45	47	42
MPAP (mmHg)	56	57	52	75
SPAP (mmHg)	88	90	35	50
PVR (mmHg l^{-1} m^{-1})	10	14	9	8
CI (lm^{-1} m^{-2})	1.82	1.71	3.21	1.93
6MWT (m)	260	270	235	556
Exitus	No	Yes	No	No
Treatment	Ambrisentan	Ambrisentan	Ambrisentan	Ambrisentan

HIV-PAH, pulmonary arterial hypertension associated with HIV; CI, cardiac index; MPAP, mean pulmonary artery pressure; SPAP, systolic pulmonary arterial pressure; PVR, pulmonary vascular resistance; 6MWT, 6-min walk test.

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