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Screening of pulmonary hypertension in a Spanish cohort of patients with systemic sclerosis☆

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ABSTRACT

Background and objective: Pulmonary arterial hypertension (PAH) is an important cause of morbimortality in systemic sclerosis (SSc). Evolution is worse than that of subjects with idiopathic PAH, but prognosis improves when PAH is diagnosed early. The aim of this research is to describe results of a screening program for diagnosis of pulmonary hypertension (PH) carried out in a cohort of Spanish patients with SSc.
Patients and method: PH screening was performed by transthoracic Doppler echocardiography (TTDE) in 184 patients with SSc. Patients with systolic pulmonary arterial pressure estimated by TTDE > 35 mmHg were evaluated per protocol to confirm diagnosis and type of PH.
Results: PAH was diagnosed in 25 patients (13.6%). Patients with diffuse and limited SSc developed PAH in a similar degree, 9/60 (15%) vs. 16/100 (16%), with no cases among patients with SSc "sine scleroderma" or "pre-scleroderma" ($p < .001$). The only clinical or epidemiological data characterizing patients with PAH were older age (mean age 67 years for patients with PAH vs. 56 years for those without PAH, $p = .007$), limited SSc, a trend towards shorter evolution of the underlying disease (median 8 years for patients with PAH vs. 10 years for those without PAH, $p = .73$), and a higher frequency of positive anticentromere antibodies (16 patients [64%] with PAH vs. 70 (48.3%) without PAH, $p = .19$).
Conclusions: Prevalence of PAH in SSc was high and supports the implementation of a regular screening program.

Cribado de hipertensión pulmonar en una cohorte española de pacientes con esclerosis sistémica

Palabras clave:
Esclerosis sistémica
Hipertensión pulmonar
Cribado

RESUMEN

Fundamento y objetivo: La hipertensión arterial pulmonar (HAP) es causa importante de morbimortalidad en la esclerosis sistémica (ES). Su evolución es peor que en la HAP idiopática, pero el pronóstico mejora si se diagnostica precozmente. El objetivo de este trabajo es describir el resultado de un programa de cribado para el diagnóstico de hipertensión pulmonar (HP) desarrollado en una cohorte de pacientes españoles con ES.
Pacientes y método: Se realizó cribado de HP mediante ecocardiografía-doppler transtorácica (EDTT) en 184 pacientes con ES. Los pacientes con valor de presión arterial pulmonar sistólica estimada por EDTT > 35 mmHg se evaluaron de forma protocolizada para establecer o no el diagnóstico de certeza de HP y su tipo.

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Resultados: Se diagnosticó HAP en 25 pacientes (13,6%). Los pacientes con ES difusa y limitada desarrollaron HAP en proporciones semejantes: 9 de 60 (15%) frente a 16 de 100 (16%). No se registraron casos entre pacientes con ES «sine esclerodermia» o «preesclerodermia» (p < 0,001). Los únicos datos clinicoepidemiológicos que caracterizaron a los pacientes con HAP fueron una edad más avanzada (edad media de 67 años para pacientes con HAP frente a 56 años sin HAP, p = 0,007), especialmente relacionada con la ES limitada, y una tendencia hacia un menor tiempo de evolución de la enfermedad de base (mediana de 8 años para pacientes con HAP frente a 10 años sin HAP, p = 0,73) y una mayor frecuencia de positividad para anticuerpos anticentrómero: 16 (64%) pacientes con HAP frente a 70 (48,3%) sin HAP (p = 0,19).
Conclusiones: La prevalencia de HAP en ES resultó elevada y apoya la implantación de programas de cribado sistemático.

Introduction

Pulmonary hypertension (PH) is characterized by a value of the mean pulmonary artery pressure (PAP) (mPAP) measured by right heart catheterization (RHC) ≥ 25 mmHg at rest, secondary to an obstacle located at any point of the pulmonary vascular circuit. Pulmonary arterial hypertension (PAH), a PH variant secondary to proliferation-obstruction of the pulmonary arterioles and characterized by an increase in PAP in the absence of involvement of the left side of the heart or pulmonary parenchymal or thromboembolic disease, is a serious complication and relatively common in patients with systemic sclerosis (SSc).[1] Initial studies found that the progression of these patients and their response to vasodilator treatment was worse than that observed in individuals with idiopathic PAH (IPAH). Later it was shown that the prognosis improved significantly if the diagnosis of PAH was established at an early stage (ideally, during functional class [FC] I). In order to establish a diagnosis and appropriate treatment as early as possible, the clinical practice guidelines recommend performing periodic screening by Transthoracic Doppler echocardiography (TDE) in patients with SSc.[2,3] A system defining the risk criteria for the development of PH was recently established (PHAROS registry)[4,5] (systolic PAP [sPAP] > 40 mmHg, diffusion of carbon monoxide [DLCO] < 55% of the predicted value or a forced vital capacity [FVC]/DLCO ratio > 1.6), which gets patients diagnosed in the early functional stages with survivals of 75% at 3 years. Following these guidelines, a screening program for early detection of PAH in a cohort of patients with SSc was designed and developed, which happened to be the first work published, in this sense, among Spanish population.

Patients and method

In June 2003, a PAH screening program in a cohort of patients with controlled SSc was started in a unit which specializes in keeping both processes under control in the Virgen del Rocio hospital in Seville. Data collection was closed on June 30, 2014. In addition to the patients evaluated in this program, the patients studied before the start of the screening program for suspected PAH were also considered. For the diagnosis of SSc, the *American Rheumatism Association* 1980[6] criteria were used, initially. Depending on the type of skin involvement, the disease was classified as diffuse SSc (dcSSc), with skin sclerosis distal and proximal to elbow and knee, and limited SSc (lcSSc), with cutaneous sclerosis limited proximally by elbows and knees. It can also affect face and neck. Patients without skin involvement but with vascular impairment (defined by Raynaud's phenomenon or anomalies in nailfold capillaroscopy) and positivity for SSc specific autoantibodies (anticentromere [ACA] or antitopoisomerase I [ATA-I]) were considered affected by "sine scleroderma SSc" (ssSSc) if there was evidence of established visceral condition characteristic of SSc (gastrointestinal hypomotility, interstitial lung disease [ILD], PAH, scleroderma renal crisis or heart disease), or "pre-scleroderma" (pre-SSc) in case of suffering from Raynaud's phenomenon with SSc specific antibodies and/or capillaroscopic anomalies.[7,8] Determining autoantibodies both antinuclear (ANA) as well as specific to SSc (ACA y ATA-I) was performed by immunofluorescence using HEp-2 as substrate (ANA and ACA) and by immunodiffusion or counterimmunoelectrophoresis (ATA-I). Patients were systematically assessed each year in the case of remaining asymptomatic, but that review was brought forward if the symptoms appeared. Systematic screening is summarized in Fig. 1. In each review, the presence of PAH symptoms or signs (dyspnoea, angina, syncope, and right heart failure) was evaluated. A TDE, a chest X-ray and respiratory function tests (RFTs) with determination of FVC and DLCO were performed in all patients yearly. More recently, the protocol included the *N-terminal pro-brain natriuretic peptide* (NT-proBNP) determination. It was considered that the sPAP, evaluated by TDE, was high if its value (resulting from the formula $sPAP = 4V^2 + DBP$; V being the maximum speed of tricuspid regurgitation [TRV] and DBP the mean right atrial pressure, evaluated according to the echocardiographer's interpretation) was higher than 35 mmHg.[2] Depending on the clinical and echocardiographic data (sPAP ≥ 50 mmHg, sPAP > 35 mmHg in the presence of unexplained dyspnoea or a FVC/DLCO ratio > 1.8, or, more recently, a value of NT-proBNP > 200 pg/ml) it was decided to continue monitoring (when the conditions mentioned were met) or initiate a standardized study to establish or rule out a definitive diagnosis of PAH (Fig. 1). The assessment of potential ILD was carried out by chest radiography, RFTs (FVC < 70% of predicted value) and high resolution computed tomography (HRCT), if considered appropriate; the assessment of venous thromboembolism was performed by pulmonary scintigraphy and/or angio-CT of the thorax; other tests (such as polysomnography) if the medical history recommended it. Finally, we conducted a RHC to establish or exclude the diagnosis of PH with certainty, excluding only those patients in whom it was considered that the PH was undoubtedly associated with left heart failure (clinical and radiologic assessment and indicative TDE data, such as ejection fraction of the left ventricle [LVEF] < 50% as an expression of systolic dysfunction, mitral or aortic valvular dysfunction of at least moderate grade or significant parameters of diastolic dysfunction according to the echocardiographer) or with advanced pulmonary fibrosis (significant changes in HRCT with FVC < 70% and FVC/DLCO ratio < 1.8). The existence of PH was considered by RHC when the mPAP at rest was ≥25 mmHg, distinguishing between precapillary PH when pulmonary capillary pressure (PCP) was ≤15 mmHg, and when the postcapillary PCP was >15 mmHg. PAH was considered confirmed when the requirements for precapillary PH were met in the RHC, with FVC > 70% or DLCO value disproportionately low in relation to that one's value (FVC/DLCO > 1.8). PAH was considered potential when patients had a sPAP value >35 mmHg and ≤50 mmHg in the TDE, being asymptomatic and without evidence of significant respiratory or cardiac dysfunction. In patients with exertional dyspnoea not justified by