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The association between BNP, 6MWD test, DLCO% and pulmonary hypertension in sarcoidosis

Mehdi Mirsaeidi[1], Hesham R. Omar[2], Robert Baughman[3], Roberto Machado[4], Nadera Sweiss[4]

[1] Division of Pulmonary, Critical Care, Sleep and Allergy, Department of Medicine, University of Miami, FL, USA; [2] Internal Medicine Department, Mercy Medical Center, Clinton, Iowa, USA; [3] Department of Medicine, University of Cincinnati, OH, USA; [4] Division of Pulmonary, Critical Care, Sleep and Allergy, Department of Medicine, University of Illinois at Chicago, IL, USA

Abstract. *Introduction:* Pulmonary hypertension (PH) is a feared complication in patients with sarcoidosis.It is an important negative prognostic factor which is reflected as a priority given to these subjects for orthotopic lung transplantation. We evaluated the relationship between BNP, 6MWD test, DLCO% values and the severity of sarcoidosis-associated pulmonary hypertension. *Methods:* A retrospective chart review was conducted between January 2010 and January 2015 on consecutive confirmed adult subjects diagnosed with sarcoidosis. Demographics, medical comorbidities, clinical features, pulmonary function tests (PFTs), 6MWD test, transthoracic echocardiography, laboratory investigations, radiographic findings, treatment and outcome data were collected from medical records. Subjects with suspicion for PH (i.e. those with PASP ≥ 25 mmHg) were included in the study. PH severity was classified using PASP into mild (PASP 25-49 mmHg), moderate (50-69 mmHg) and severe (≥70 mmHg). We evaluated the strength of correlation between BNP, 6MWD test, DLCO% and the severity of PH. The association between variables was performed using Pearson correlation coefficient and results were considered statistically significant if P value was <0.05. *Results:* Among the 108 cases diagnosed with sarcoidosis, we identified a total of 27 patients (25%) who had an elevated PASP suggestive of PH and met the study inclusion criteria. There was a significant correlation between BNP level (r=0.804, P=0.003), 6MWD test (r=-0.865, P=0.000), DLCO% (r=-0.513, P=0.015) and the PASP in sarcoidosis patients. *Conclusion:* Although these simple tests should not be used as screening tools for suspecting sarcoidosis-associated pulmonary hypertension, they may be of value in following its progression in subjects already diagnosed with pulmonary hypertension. *(Sarcoidosis Vasc Diffuse Lung Dis 2016; 33: 317-320)*

Key words: sarcoidosis, pulmonary hypertension, pulmonary function test, BNP, 6-minute walk distance test

Introduction

Pulmonary hypertension (PH) is a feared complication in patients with sarcoidosis as it is an important negative prognostic factor which is reflected in the added priority given to these subjects for orthotopic lung transplantation (1-3). It has also been observed that patients with an elevated estimated pulmonary artery systolic pressure (PASP) have an increased mortality versus those with lower estimated pressure (4). The gold standard in diagnosing PH is the direct measurement of the pulmonary artery pressure with right heart catheterization (RHC) (5). Transthoracic echocardiogram (TTE) is used as noninvasive test for the initial evaluation of suspected PH as it correlates well with catheterization values (r=0.93) (6) but this

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Correspondence: Mehdi Mirsaeidi MD, MPH
Division of Pulmonary, Critical Care, Sleep and Allergy,
Department of Medicine, Division of Pulmonary,
Critical Care, Sleep and Allergy, Department of Medicine
University of Miami, Miller School of Medicine
1600 NW 10th Ave # 7060A Miami, FL 33136
E-mail: msm249@med.miami.edu

test cannot replace RHC for PH diagnosis. The coefficient of correlation between pulmonary artery pressure measured by TTE or RHC is stronger in patients with an estimated pulmonary artery pressure of greater than 50 mm Hg (4-6). Other non-invasive tests like the six-minute walk distance (6MWD) (7, 8) and the need for supplemental oxygen (9) were shown to be independent predictors of PH in sarcoidosis patients. In this study, we aim to evaluate the strength of association between brain natriuretic peptide (BNP), 6MWD test, diffusion capacity for carbon monoxide (DLCO%) and the severity of sarcoidosis-associated pulmonary hypertension estimated by TTE.

Methods

A retrospective chart review was conducted between January 2010 and January 2015 on consecutive adult subjects diagnosed with sarcoidosis according to the European Respiratory Society (ERS), American Thoracic Society (ATS) and World Association of Sarcoidosis and other Granulomatous Disorders (WASOG) criteria (2) with collection of data related to patient demographics, medical comorbidities, clinical features, pulmonary function tests (PFTs), 6MWD test, TTE, laboratory investigations, radiographic findings, treatment and outcome. The Institutional Review Board of the University of Illinois at Chicago approved the study and waived the need for patient consent (approval number of 20130195001). Subjects with suspicion for PH (i.e. those with PASP ≥ 25 mmHg) were included in the study. Estimated PASP was diagnosed with TTE and calculated based on the modified Bernoulli equation where it is equivalent to the right ventricular systolic pressure (measured by the addition of transtricuspid gradient plus an estimate of the right atrial pressure) (5). Subjects with an ejection fraction of less than 50% were excluded from the analysis. PH severity was classified using PASP into mild (PASP 25-49 mmHg), moderate (50-69 mmHg) and severe (≥70 mmHg). We evaluated the strength of correlation between BNP, 6MWD test, DLCO% and the severity of PH. Data were analyzed using IBM SPSS 21.0 statistical software (IBM SPSS Version 21.0. Armonk, NY). The association between variables was performed using Pearson correlation coefficient and results were considered statistically significant if P value was <0.05.

Results

Among the 108 cases diagnosed with sarcoidosis, we identified a total of 27 patients (25%) who had an elevated PASP suggestive of PH and met the study inclusion criteria. Among the group of patients with sarcoidosis-associated PH, the mean age was 57.4 years, 81% were females, 81.5% were African Americans, the average sarcoidosis duration was 14 years and the mean ejection fraction was 58±4.4. Two cases had severe PH, 4 had moderate PH and 21 had mild PH. The average estimated PASP by TTE was 41.2±17.9 mmHg. Among these 27 subjects with PH, the DLCO% was decreased to 61±18.6% while forced vital capacity (FVC%) remained 83.5±25.35% with a FVC%/DLCO% ratio of 1.45±0.5. The 6MWD test was 364±77 meter and average oxygen saturation on room air was 94±3%. 88.5% of subjects were on oral steroids, 33% on disease-modifying antirheumatic drugs (DMARDs), 18.5% on methotrexate, 14.8% on sildenafil, and 3.7% on treprostinil. At 3-year follow up 23 cases were alive and no mortality data could be obtained regarding the 4 remaining cases. Correlation analysis on the 27 patients diagnosed with PH showed a strong significant association between the BNP level and the PASP (r=0.804, P=0.003). There was also a strong significant inverse correlation between the 6MWD test and the PASP (r=-0.865, P<0.0001) and a moderate significant inverse correlation between the DLCO% and the PASP (r=-0.513, P=0.015). Table 1 lists the patients' demographics, clinical characteristics, PFTs, transthoracic echocardiography data and selected treatment modalities of the study population.

Discussion

This retrospective analysis of a cohort of sarcoidosis patients with PH showed a significant association between BNP level, 6MWD and DLCO% and the PASP. The strength of correlation coefficients encountered in our analysis is encouraging and suggest that in patients with already diagnosed PH -with other more sensitive and specific diagnostic modalities-, a follow up of BNP, 6MWD test and DLCO% may indirectly provide information about the progression of PH. Unfortunately serial assessments of pulmonary pressures by RHC cannot be

Table 1. Demographics, clinical characteristics, pulmonary function tests results, echocardiography and right heart catheterization data and selected treatment modalities of the study population with sarcoidosis-associated pulmonary hypertension

Demographics and clinical characteristics	
Age (y)	57.4±8.9
Female sex n (%)	22 (81.5%)
BMI (m±SD)	31.2±7.3
African American race n (%)	22 (81.5%)
Current smokers n (%)	2 (7.7%)
Extrapulmonary sarcoidosis n (%)	16 (59.3%)
DM n (%)	5 (17.9%)
Hypertension n (%)	20 (71.4%)
COPD n (%)	6 (22%)
Cough n (%)	14 (51.9%)
Dyspnea n (%)	18 (69.2%)
6MWD test (meter, m±SD)	364.4±77.3
Duration of sarcoidosis (year, m±SD)	14.1±10.8
Pulmonary function tests	
FVC%	83.5±25.3
FEV1%	74.3±28.5
VC%	88±23.9
DLCO%	61±18.6
TLC%	84.3±17.1
FRC%	101.6±20.6
RV%	99.9±29.1
FVC%/DLCO%	1.45±0.5
Echocardiography and laboratory values	
Ejection fraction (m±SD)	58±4.4
PASP by TTE (mmHg, m±SD)	41.3±18
Laboratory values	
BNP (pg/mL, m±SD)	390±868
ACE level (mcg/L)	69.8±65.1
Treatment	
Oral steroids n (%)	23 (88.5%)
DMARD n (%)	9 (33.3%)
Methotrexate n (%)	5 (18.5%)
Sildenafil n (%)	4 (14.8%)
Treprostin n (%)	1 (3.7%)

BMI: body mass index, COPD: chronic obstructive pulmonary disease, 6MWD: 6-minute walk distance, PASP: pulmonary artery systolic pressure, BNP: brain natriuretic peptide, PAP: pulmonary artery pressure, PCWP: pulmonary capillary wedge pressure, DMARD: disease-modifying antirheumatic drugs, TTE: transthoracic echocardiogram, RHC: right heart catheterization, ACE: angiotensin converting enzyme, n: number, m: mean, SD: standard deviation.

used to follow PH in sarcoidosis subjects as it is invasive.

The study did find that BNP levels correlated with the severity of pulmonary hypertension as estimated by TTE. Increased BNP levels can occur in the setting of either left or right ventricular strain. In sarcoidosis, pulmonary hypertension has multiple potential causes including pre and post-capillary etiologies (4). Echocardiographic findings consistent with moderate to severe pulmonary hypertension in sarcoidosis patients were associated with increased mortality (4). Therefore the finding of an elevated BNP may be important regardless of the cause.

This study confirmed that a reduced DLCO is seen with a pulmonary hypertension. The lower the DLCO, the more severe the pulmonary hypertension. However, since reduced DLCO can be due to multiple factors, this test may not be a useful screening test in fibrotic sarcoidosis. We have observed that the FVC% remained unaffected suggesting that in sarcoidosis-associated PH, the DLCO falls disproportionately to FVC (FVC%/DLCO% ratio was 1.45). This was shown by others who found an inverse relationship between the pulmonary artery pressure and the FVC in sarcoidosis patients (10). This should be further tested in comparative studies to find a cutoff ratio that would raise suspicion for PH in sarcoidosis as this ratio may be a better tool compared with a reduction in DLCO alone (as in sarcoidosis-associated interstitial lung disease, both FVC and DLCO will fall proportionately, while in PH DLCO falls disproportionately to FVC).

The study limitations include the relatively small cohort, the retrospective design nature and the lack of RHC data for all patients. We may have also missed patients who have PH but without a visible tricuspid regurge jet on TTE. Because our main aim was to study the strength of association between BNP, 6MWD test, DLCO% and PASP to assess the value of these tests in following up patients with already diagnosed PH –rather than identifying predictors of PH-, we therefore did not include a control group. Also, in some patients, there may have been time difference between various studied parameters so not all data are contemporaneous.

Conclusion

Although simple tests like BNP, 6MWD test and DLCO% should not be used solely as screening tools for diagnosing sarcoidosis-associated PH, they may be of value in following up its progression in subjects already diagnosed with PH. Further larger trials are needed to confirm these results.

Author Contributions:

Conception, hypotheses delineation, and design of the study: M.M. H.R.O The data analysis and interpretation of such information: M.M., H.R.O., Writing the article or substantial involvement in its revision before submission: M.M, H.R.O., R.B, R.M, N.S

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