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N-terminal pro-brain natriuretic peptide is a strong predictor of mortality in systemic sclerosis

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ABSTRACT

Objectives: Cardiovascular involvement is a major contributor to mortality in systemic sclerosis (SSc). We examined whether N-terminal pro-brain natriuretic peptide (NT-proBNP) is a reliable predictor of mortality in SSc.
Methods and results: This multicentre prospective cohort study included 523 patients presenting with SSc, whose mean age was 54 ± 13 years, mean disease duration 8 ± 9 years, and diffuse cutaneous form in 168. Plasma NT-proBNP was measured at baseline and the patients were followed yearly. Overall mortality was measured at 3 years. At baseline, cardiovascular involvement was present in 37 patients, including 17 with pulmonary artery hypertension (PAH) and 20 with a left ventricular ejection fraction (LVEF) <55%. At 3 years, 32 (7%) patients had died. The median [25th–75th percentile] NT-proBNP concentration was 203 ng/l [129–514] in patients who died within 3 years, versus 88 ng/l [47–167] in survivors ($P < 0.001$). NT-proBNP was an independent predictor of 3-years mortality in multivariate analysis ($P = 0.046$). The optimal cut-off derived from the ROC curve was 129 ng/l; sensitivity and specificity to predict 3 y mortality were 78.1 and 66.7%. Using the previously recommended 125-ng/l concentration as threshold value, NT-proBNP reliably and independently predicted 3 year mortality, with a sensitivity of 78.1 and a negative predictive value of 97.6%, respectively ($P = 0.006$). The consideration of SSc patients without PAH or LVEF < 55% at baseline yielded similar results.
Conclusion: NT-proBNP appears as a reliable and independent predictor of mortality in patients with SSc.

1. Introduction

Systemic sclerosis (SSc) is a connective tissue disease, characterized by fibrosis of the skin and internal organs, prominent alterations of the microvasculature, frequent abnormalities of cellular and humoral immunity [1]. A previous meta-analysis reported pooled standardized mortality ratio of 3.5 (2). In a meta-analysis of 9 studies, including nearly 2700 patients suffering from SSc, 55% died of SSc-related and 41% of SSc-unrelated causes [2]. Among the SSc-related deaths, 35% were due to lung fibrosis, 26% to pulmonary arterial hypertension (PAH), 26% to heart failure, arrhythmias or both, and 4% to scleroderma renal crisis [2]. While the prognosis of SSc in large sample populations remains poor, the individual risk varies considerably, mandating an accurate and prompt identification of high-risk patients. In view of the systemic nature of the disease, precise risk stratification remains a clinical challenge.

Once SSc is clinically apparent, the presence of cardiac involvement is prognostically ominous [3]. However, while an early diagnosis is critically important, the pre-clinical identification of cardiac disease or PH in SSc remains challenging. Echocardiography and pulsed tissue

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Doppler are the best routine diagnostic tests, as they enable the detection of a depressed systolic and diastolic cardiac function, the measurement of pulmonary artery pressure (PAP), and the identification of valvular or pericardial involvement [4,5]. Since the introduction of routine assays for natriuretic peptides, B-type natriuretic peptide (BNP) and its N-terminal inactive fragment (NT-proBNP) have both been recognized as markers of myocardial wall stress and used for the diagnosis and prognosis of various disorders, including the diagnosis of reduced contractility and PAH, and in predicting the development of PAH during follow-up of SSc patients [6–9]. This study was designed to examine the prognostic significance of NT-proBNP in patients presenting with SSc.

2. Patient population and methods

Consecutive patients suffering from SSc were prospectively enrolled at 6 medical centres in France, Germany, Hungary and Italy and followed-up at regular intervals at their institution. The protocol of this prospective cohort study, which complies with the Declaration of Helsinki, was reviewed and approved by the ethics committees of all enrolling medical centres, and each patient signed an informed consent to participate. All patients were eligible to enter the study if they had been on a stable condition, including constant drug regiment during the last 3 months. Patients treated with steroids could be enrolled provided prednisone dosage was ≤10 mg/d and remained constant prior to the enrolment. SSc was classified as limited versus diffuse cutaneous sub-type, according to the criteria of LeRoy et al. [10], and disease duration was measured according to the duration since the first non-Raynaud's symptom; a detailed baseline evaluation of their disease was completed, including systematic renal, cardiac, and pulmonary biological/morphological exams. Laboratory studies obtained on the morning of hospital admission included plasma NT-proBNP concentration, complete blood cell count, serum C-reactive protein and creatinine concentrations, and tests for anti-centromere and anti-topoisomerase I antibodies. Echocardiography was performed as described in detail previously [5]. Briefly, the left ventricular (LV) ejection fraction (EF) was measured by the Simpson method. The systolic PAP was estimated by Doppler examination, based on the degree of tricuspid or pulmonary regurgitation at rest, adding 10 mm Hg of atrial pressure, as recommended. The presence of pulmonary involvement was ascertained by chest radiography, computed tomography, forced vital capacity, and the ratio of diffusing capacity for carbon monoxide (DLCO) to the alveolar volume (DLCO/AV). Right heart catheterization was performed at the discretion of the treating physician, based on criteria applied in our earlier studies, including a) an echocardiographically estimated systolic PAP >40 mm Hg, used as a screening threshold, or b) a DLCO <50% of predicted in absence of pulmonary fibrosis, or c) unexplained dyspnea. PAH was confirmed when the mean PAP was ≥25 mm Hg at rest, with a pulmonary capillary wedge pressure ≤ 15 mm Hg measured during right heart catheterization [8]. Our primary endpoint was all cause-mortality examined at 3 years of follow-up.

2.1. Follow-up and clinical outcomes

The patients were followed at 3–6 months intervals, as indicated by the severity of disease and according to their physicians' customary practice. They underwent detailed, annual evaluations, including echocardiography and pulmonary function tests. If the patient did not attend to the visit, both their relatives and the primary care physicians were contacted, the medical records of the hospitals were consulted to obtain vital status information.

The final observations were made at the last visit of year 2014 or at the last visit available before death from any cause. The database was completed and analyzed during the first semester of 2015.

2.2. NT-proBNP assay

Blood samples were collected in plastic tubes containing Lithium heparin in a patient in a supine position in an ambient room temperature for at least 30 min, from a peripheral antecubital vein. The samples were centrifuged immediately after collection, frozen at −80 °C until and the concentrations of NT-proBNP were measured in each participating centre using similar sandwich immunoassay on an Elecsys® 2010 instrument (Roche Diagnostics, Basel, Switzerland). All investigators who performed the assays were unaware of the clinical and echocardiographic observations.

2.3. Statistical analysis

Continuous variables are expressed as medians [25th–75th percentiles] and categorical variables as counts and percentages. A Cox hazards regression was performed to examine associated factors with 3-year mortality; Hazards Ratios with their 95% confidence interval are reported. Values that emerged in single variable analysis ($p < 0.05$) were then analyzed using multiple variable COX hazards regression. The role of NT-proBNP was examined in two distinct models, as a continuous variable in the first analysis (after log-transformation for the multivariable analysis) and as a discrete variable (NT-proBNP above or below the recommended threshold value of 125 ng/l) in the second analysis. This threshold value has been previously recommended in SSc as well as in other diseases for the diagnosis of reduced LVEF, PAH or both [6–9]. For multivariable analyses, all values were transformed in categorical variable, based on recommend threshold values if this item was also significant in the univariate model, or alternatively based on its median; age was divided categories of 10 y. Due to linearity between the cutaneous subset of the disease and the Rodnan skin score and missing data for the latter, only the cutaneous subset of the disease was retained in the multivariate analysis.

The performance of NT-proBNP to predict 3-year mortality was graphically reported using a Kaplan–Meier representation and receiver operator curves (ROC); an optimal NT-proBNP threshold value was determined from the ROC curve, the sensitivities, specificities and negative predictive values of NT-proBNP were determined using that concentration as well as 125 ng/l. A P value < 0.05 was considered statistically significant. The STATA statistical software, version 13.1 (StataCorp LP, College Station, TX) was used for all analyses.

3. Results

3.1. Baseline characteristics

The 6 participating medical centres enrolled 523 patients (323 women), whose mean age was 54 ± 13 years and mean disease duration 8 ± 9 years. The baseline characteristics of the study population are shown in Table 1. The cardiovascular system was involved in 37 patients, including proven PAH in 17 and a LVEF <55% in 20. No patient presented with renal insufficiency.

3.2. Clinical outcomes

The mean follow-up was 54 ± 32 and median 53.2 [25.0–83.0] months; Follow-up was complete at 1 year in 509 patients, at 2 years in 486 patients and at 3 years in 458 patients. Vital status was obtained in all patients at the time of completion of the database. Among these 458 patients, 426 (93.0%) were alive and 32 (7.0%) had died.

3.3. Prediction of mortality

The median concentration of NT-proBNP was 203 ng/l [129–514] in patients who died, versus 88 ng/l [47–167] in survivors ($P < 0.001$). The plasma concentration of NT-proBNP was >125 ng/l (the previously