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Prevalence of wild type ATTR assessed as myocardial uptake in bone scan in the elderly population

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ABSTRACT

Background: Myocardial uptake of bone tracers has emerged as useful tool for the early detection of transthyretin amyloidosis (ATTR). The prevalence of wild-type ATTR (ATTRwt) in individuals remains to be established.

Methods: All whole body bone scans performed in individuals ≥ 75 years with no previous clinical suspicion of ATTR were revised in a population-based university hospital over a 7-year period (1509 studies corresponding to 1114 patients; 80.5 ± 4.1 years, 65% males). Positive cardiac uptake was defined according to Perugini score as grade 2 or 3. Heart failure (HF) hospitalizations during the follow-up were obtained from regional administrative databases.

Results: Thirty-one patients ≥ 75 years (2.78%) showed cardiac uptake; compared with those without uptake, these patients were older (85 ± 5 vs. 80 ± 4 , $p < 0.001$) and predominantly males (90% vs. 64%, $p = 0.005$). The prevalence of cardiac uptake was 3.88% in males and 0.77% in females, and increased with age, reaching 13.9% in males ≥ 85 years (2.7% among females). The estimated prevalence for the European standard population ≥ 75 years was 4.15% in males, 1.03% in females and 2.59% in the general population. HF hospitalization rates were 14% in patients without uptake and 29% in those with cardiac uptake ($p = 0.034$). After adjusting for age and gender, cardiac uptake was associated with a higher risk of HF hospitalization (OR 2.60, 95%CI 1.09–5.74, $p = 0.022$).

Conclusions: Myocardial uptake in bone scan is very prevalent with ageing, mainly affects males and is associated with an increased risk of HF hospitalization. These findings reinforce ATTRwt as a relevant cause of HF in the elderly.

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1. Introduction

Amyloidosis is a disorder caused by the extracellular deposition of insoluble abnormal fibrils composed of misfolded proteins. Light chain (AL) and Transthyretin (ATTR) are the most frequent types of amyloidosis. ATTR may be hereditary due to variants in the TTR gene, or

acquired due to deposition of wild-type transthyretin (ATTRwt). The latter was formerly known as senile amyloidosis and almost exclusively affects the heart, causing myocardial infiltration and/or direct toxicity, leading to diastolic and systolic dysfunction, heart failure (HF), rhythm disturbances and ischemia [1–3]. ATTRwt has traditionally been considered a rare disease, but it has probably been largely underrecognized. Recently, ATTRwt has been reported as a frequent cause of HF with preserved ejection fraction (HFpEF) and also as a prevalent disease among elderly individuals with severe aortic stenosis undergoing TAVI replacement [4–7].

Cardiac retention of technetium-labeled bone tracers on bone scintigraphy has demonstrated to be a highly sensitive and specific tool for detecting ATTR [8]. Gillmore et al. have shown that moderate-

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severe cardiac uptake (Perugini grade 2–3) on bone scan is highly sensitive (90%) and specific (97%) for cardiac ATTR [9]. Moreover, the combination of grade 2–3 cardiac uptake on bone scan, together with the absence of a detectable monoclonal protein, was 100% specific and had a 100% positive predictive value for cardiac ATTR diagnosis [9]. Furthermore, bone scintigraphy allows early identification of cardiac TTR amyloid deposits in asymptomatic patients before the development of HF clinical symptoms or other abnormalities identified by echocardiography or CMR [10]. Although autopsy studies have shown the presence of myocardial ATTR in up to 25% of subjects over 80 years of age [11], the prevalence of ATTRwt in the elderly population and the impact on HF development remains unknown.

The aims of this study were to determine the prevalence of cardiac uptake of technetium-labeled bone tracers among elderly patients without previous suspicion of cardiac amyloidosis, and to investigate the association between myocardial uptake and HF hospitalization.

2. Methods

2.1. Study population and whole body scintigraphy

We retrospectively reviewed all the whole body bone scans performed on patients ≥ 75 years between 2010 and 2016, at the University Hospital Virgen de la Arrixaca (Murcia, Spain) a reference center for nuclear medicine studies and serving for the whole of the province of Murcia in Southwest Spain. A total of 1509 whole body bone scans, corresponding to 1114 patients, were assessed (Fig. 1S, supplementary material). All the scans were performed for oncologic (95.7%) and rheumatologic reasons (4.3%) and none was requested for the clinical suspicion of cardiac amyloidosis. Planar whole-body bone scintigraphy was performed between 2 and 3 h after intravenous injection of 740 MBq of Technetium-99 m labeled bone tracers: 196 (13%) studies were performed with Tc99m-DPD (3,3-diphosphono-1,2-propanodicarboxylic acid), 604 (40%) with Tc99m-HDP (hydroxyethylene diphosphonate) and 709 (47%) with Tc99m-HMDP (hydroxymethylene diphosphonate). Anterior and posterior whole-body images were acquired on a dual-head gamma camera (Infinia Hawkeye 4, GE Healthcare; or Philips Skylight AZ, Philips Healthcare), with low-energy high-resolution collimators, in a matrix of 256×1024 at a table speed of 10 cm/min. Myocardial tracer uptake was graded according to the Perugini visual score, taking into account the uptake in both ventricles compared with the adjacent rib uptake. Positive cardiac uptake was defined as grades 2 (equal to the rib uptake) and grade 3 (greater than the rib uptake) (examples are showed in Supplemental material, Figs. 1S and 2S) [8]. Scans were interpreted independently by two experienced nuclear cardiologists blinded to patient data, from two different centers (M-L and FJ-HM), and discrepancies were resolved by consensus.

2.2. Clinical evaluation

The occurrence of HF hospitalizations, both prior to or following scintigraphy, was investigated in all subjects by consulting the administrative clinical database set CMBD,

which is an obligatory register that includes all public and private hospitals in the province of Murcia. In all patients with cardiac uptake ($n = 31$), clinical records of all patients with cardiac uptake were revised retrospectively and clinical characteristics, including history of carpal tunnel syndrome and treatments were recorded. In addition, among survivors, eleven patients accepted to be investigated at the Heart Failure Unit of Hospital Universitario Virgen de la Arrixaca at the time of the study. The study in this subgroup ($n = 11$) included blood tests, ECG and transthoracic echocardiography. In this subgroup, AL amyloidosis was excluded by immunofixation electrophoresis of serum and urine and by the serum free light chain assay; a mutation in TTR gene was also excluded by genetic analysis. Blood chemistry parameters, including creatinine, protein, troponin T, N-terminal pro-T-type natriuretic peptide (NT-proBNP), hemoglobin, serum ferritin, and transferrin saturation, were measured by standard automated commercial techniques. ECG and echocardiographic measures were based on standard definitions, as previously reported [2].

2.3. Statistical analysis

Categorical variables are expressed as frequency (percentage) and continuous variables as mean (standard deviation, SD) or median [quartiles, Q1–Q3], as appropriate. The prevalence of cardiac uptake was also calculated according to the population distribution in the Region of Murcia official census (http://econet.carm.es/inicio/-/crem/sicrem/PU_padron/p16/sec2_sec2.html; updated February 6th, 2017) and the European standard population (<http://ec.europa.eu/eurostat/web/population-demography-migration-projections/population-data/main-tables>). As exploratory analysis, Fisher's exact test was used to contrast differences in frequencies, and an ANOVA or Kruskal–Wallis test was used to contrast differences in means or distributions, as appropriate. Logistic regression analysis was used to assess the association of cardiac uptake and HF hospitalization, adjusting by sex and age. All the statistical analyses were performed using R statistical software (version 3.4.2).

3. Results

3.1. Myocardial Tc99 uptake prevalence

A total of 1114 patients ≥ 75 years were studied (80.54 ± 4.13 years, median 80.07, IQR: 77.40–82.95, 65% males). Among the 1114 subjects, 31 (2.78%) exhibited cardiac uptake in the scintigraphy: grade 2 uptake was found in 9 (0.81%) and grade 3 in 22 (1.97%). No differences existed between tracers ($p = 0.449$). We found a significant interaction with age and gender. Regarding age, patients with cardiac uptake were significantly older (84.67 ± 4.06 years) than those with no uptake (80.42 ± 4.06 years) ($p < 0.001$). As regards gender, males represented 64.1% of subjects with no-uptake, but 90.3% of those with uptake ($p = 0.005$); the prevalence of cardiac uptake was 3.88% (28/722) in males and 0.77% ($n = 3/392$) in females in the entire population (Fig. 1). The distribution of subject with cardiac uptake by quintiles of age and by gender is shown in Fig. 2; most of cases were found in octogenarians,

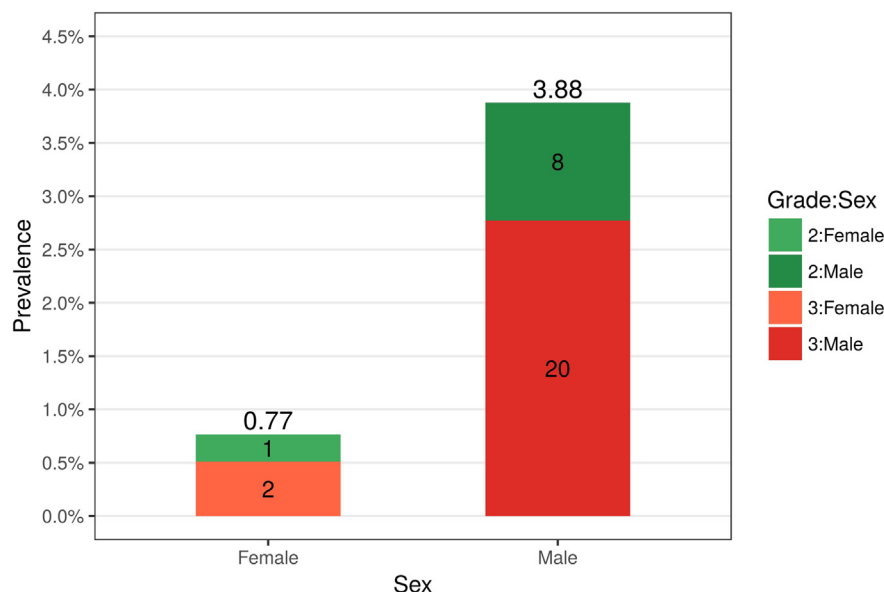


Fig. 1. Prevalence of cardiac uptake in bone scan by gender in subjects over 75 years.

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