Prevalence of Positive $^{99}$Tc-DPD Scintigraphy as an Indicator of the Prevalence of Wild-type Transthyretin Amyloidosis in the Elderly

Hyue Mee Kim, MD, Dae-Won Sohn, MD and Jin Chul Paeng, MD

Summary

Senile or wild-type transthyretin (wtTTR) amyloidosis is an age-related disease caused by the deposition of wtTTR amyloid protein. In contrast to light chain amyloidosis, $^{99}$Tc-DPD scintigraphy (DPD scan) is a useful diagnostic modality for wtTTR amyloidosis.

We retrospectively analyzed patients older than 30 years who underwent DPD scanning for non-cardiac reasons at our hospital between June 2014 and March 2017 ($n = 9,581$). Transthoracic echocardiography was used to assess left ventricular hypertrophy (LVH), as well as systolic and diastolic function.

A positive DPD scan was observed in only six patients (0.06%). All six of these patients were older than 70 years, and they constitute only 0.4% of patients in this age group (6/1652). Among the patients with a positive DPD scan, four showed concentric LVH and two showed a normal wall thickness. With respect to the severity of diastolic dysfunction and pulmonary artery pressure, patients with a positive DPD scan showed the expected E’ and pulmonary artery systolic pressure for their age.

Even considering the limited sensitivity of a positive DPD scan detecting wtTTR amyloidosis, the incidence of a positive DPD scan in non-cardiac patients indicated that wtTTR amyloid deposition does not seem to be a major cause for age-related diastolic dysfunction, nor does appear to have a high incidence in patients with heart failure with preserved EF in the elderly.

Key words: Diastolic dysfunction, Heart failure with preserved ejection fraction

Amyloidosis is a systemic disease caused by the deposition of abnormal proteins, known as amyloids, resulting in the impairment of organ function. Based on the type of amyloid deposits, amyloidosis is classified into subtypes, each showing a different prognosis and requiring different treatment. Three types of proteins are responsible for nearly all cardiac amyloidosis: immunoglobulin light chain (AL), serum amyloid A protein (SAA) and transthyretin (TTR). There are two types of TTR amyloidosis: hereditary amyloidosis associated with mutations in gene coding for TTR, and wild-type TTR (wtTTR) amyloidosis. wtTTR amyloidosis is an age-related disease, thus called senile amyloidosis, in which the TTR protein gets structurally dissociated and mis-assembled into amyloid fibrils. Previous studies have reported the prevalence of wtTTR amyloidosis increases with age, and that prevalence is estimated to be approximately 10%-25% in patients over 80. However, there exists a large gap between the incidence of wtTTR amyloidosis reported by those studies and those diagnosed clinically in our daily practice.

Cardiac amyloidosis has been diagnosed in two ways. Demonstrating amyloid deposition in an endomyocardial biopsy specimen or demonstrating cardiac involvement using various imaging modalities when systemic deposition of amyloid can be documented in other organs. Among the various imaging modalities used to detect cardiac involvement, the $^{99}$Tc-3,3-diphosphono-1,2-propanodicarboxylic acid ($^{99}$Tc-DPD) scintigraphy (DPD scan) is reported to be useful in the diagnosis of wtTTR amyloidosis.

Recently suggested high incidence of wtTTR amyloidosis in the elderly, who are not defined as the selected group of heart failure with preserved ejection fraction (HFpEF), leads us to think that wtTTR amyloidosis might be a frequent cause for age-related diastolic dysfunction.

It is conceivable that incipient wtTTR amyloidosis is a major cause for age-related diastolic dysfunction, because wtTTR is a normally existing protein. However, there are many cellular components that can be affected by aging process, such as various sarcomere proteins and ion-channels. For the better estimation of this situation,
we should determine the incidence of wtTTR amyloidosis in the elderly general population.

In addition, it has been suggested that there are relatively high incidence of wtTTR amyloidosis in elderly patients with HFrEF. Excluding a minor group of patients with known etiologies, the major group of the elderly patients with HFrEF comprises symptomatic patients with diastolic dysfunction without known etiology. This major group of patients is considered symptomatic patients with age-related diastolic dysfunction unless we can define the possible etiology. Therefore, high incidences of unrecognized wtTTR amyloidosis in elderly patients with HFrEF would be reflected in the incidence of asymptomatic patients with age-related diastolic dysfunction.

We already have a large volume of DPD scan data for non-cardiac patients. Although it might be suboptimal, we think that these patients represent normal subjects in the detection of unrecognized cardiac disease, and can represent the general population with respect to number, age, and sex distribution.

**Methods**

**Study population:** Our study population comprised patients who underwent a DPD scan for non-cardiac reasons between June 2014 and March 2017 at the Seoul National University Hospital. We excluded patients aged ≤ 30 years and the total study population comprised 9,580 patients. This study was approved by the Clinical Research Institute of The Seoul National University Hospital.

**99mTc-DPD scan and transthoracic echocardiography:** Scintigraphy was performed by intravenous administration of 740 MBq of 99mTc-DPD. 99mTc-DPD is one of two agents usually used for bone scans. Therefore, this scan has frequently been called “bone scan.” Whole body scans were obtained five minutes (early) and three hours (delayed) after injection. Grading of cardiac uptake was defined visually based on previous studies (grade 0: absent cardiac uptake and normal bone uptake, grade 1: mild cardiac uptake, inferior to bone uptake, grade 2: moderate cardiac uptake accompanied by attenuated bone uptake, grade 3: strong cardiac uptake with mild/absent bone uptake). Suspected TTR amyloidosis with a positive DPD scan was defined as DPD scan uptake grade 2 or 3. Echocardiographic images were obtained with commercially available equipment. Diastolic functions were classified into normal, relaxation abnormality, pseudonormal and restrictive physiology. Diastolic dysfunction was defined when the diastolic function was not normal. In obtaining mitral annulus velocity, the sample volume was located at the septal side of the mitral annulus. Scanning for all patients was performed by experienced sonographers based on the guidelines of the American Society of Echocardiography.

**Statistical analysis:** All statistical analyses were performed using IBM SPSS Version 22 (IBM, Armonk, NY, USA). Scatter plots were used to demonstrate a linear correlation between the indicators of diastolic dysfunction and age.

**Results**

**Clinical prevalence of latent wild-type transthyretin amyloidosis:** Of the 9,580 patients who underwent a DPD scan, a positive result for wtTTR amyloidosis was observed in six patients (0.06%); three patients with grades 2 and 3, respectively. No patients under the age of 70 showed a positive DPD scan. Among these six patients, five patients were men and the mean age was 80.7 ± 7.5 years. The prevalence of a positive DPD scan in patients in their 70s, 80s, and 90s were 0.22%, 0.7%, and 10%, respectively, with a gradual increase noted with increasing age (Figure 1). Other clinical data for patients with a positive DPD scan are summarized in the Table. Among the patients with a positive DPD scan, four showed an abnormal electrocardiogram: a low-voltage and left axis deviation (LAD) in one, LAD in one, and ST-T changes in two. An echocardiographic examination was performed in the six patients with a positive DPD scan and revealed that all patients showed diastolic dysfunction, and four demonstrated an increase in left ventricular (LV) wall thickness (≥ 12 mm). The remaining two patients did not show any noticeable findings on echocardiographic examination other than a relaxation abnormality (Table, patient 4 and 5) (Figure 2).

Among the patients with a positive DPD scan, cardiac magnetic resonance imaging (CMR) was performed in two patients and an endomyocardial biopsy in one patient. CMR findings revealed a non-ischemic pattern of late gadolinium enhancement in both patients. The endomyocardial biopsy demonstrated TTR amyloidosis in the sole patient who underwent this examination.

**Diastolic dysfunction in wild-type transthyretin amyloidosis:** Echocardiography was performed in 1,159 (12.1%) of the 9,580 patients enrolled in the study. Among these 1,159 patients, 789 (68.1%) demonstrated diastolic dysfunction and 28 patients showed LV wall thickness ≥ 12 mm. Scatter plots demonstrated that in the patients with a positive DPD scan, the early diastolic mitral annulus velocity (E’) and pulmonary artery systolic pressure showed expected values for their age (Figure 3).

**Discussion**

In this study, we demonstrated that the prevalence of a positive DPD scan in the elderly, indicating the possibility of clinically incipient wtTTR amyloidosis, was lower than the recently suggested incidence of wtTTR amyloidosis in the elderly. In patients showing a positive DPD scan, E’ velocity and estimated pulmonary artery systolic pressure showed expected values for their ages.

There have been several autopsy studies reporting the prevalence of cardiac amyloidosis. These studies have reported that TTR amyloid deposition has been detected in up to approximately 25% of the elderly population. Therefore, wtTTR amyloidosis can be considered a highly prevalent but under-recognized disease in elderly patients. In the present study, there were no patients with a positive DPD scan under the age of 70. Therefore, we can quite convincingly confirm the current belief that wtTTR amyloid deposition is an age-related process. However, only
0.4% of patients aged over 70 (6/1652) showed a positive DPD scan. Even if we assume the sensitivity of the DPD scan is much lower than currently estimated,\textsuperscript{9,10,18} the prevalence of wtTTR amyloidosis in elderly patients demonstrated by autopsies does not seem to reflect true prevalence in the general population.

Racial differences could also play a role in the variability of the prevalence of wtTTR amyloidosis among studies. An autopsy study from Japan has reported the prevalence of systemic wtTTR amyloidosis to be 6% and 11.5% in the individuals over 70 and 80 years, respectively,\textsuperscript{19} which is lower than the studies on Caucasian patients. However, no additional autopsy studies have been reported in Asians; thus, we cannot conclusively comment...
Figure 2. Scintigraphic and echocardiographic findings in patient no. 5. A 84 year-old man showing cardiac uptake in 99mTc-DPD scan without abnormal finding other than diastolic dysfunction in echocardiography. A: Positive 99mTc-DPD scan showing biventricular uptake in anterior and posterior views. B: Wall thickness in echocardiography, C: Mitral inflow pattern, D: Mitral annulus velocity, E: Tricuspid regurgitant jet by CW Doppler.

Figure 3. Relationship between age and variables of diastolic function.

on racial differences.

Additionally, an Italian cohort study, performed in a similar manner to our present study, has shown the rate of myocardial uptake was similarly low to the rate we reported in our study (1.4% among men older than 80 years). HFrEF is associated with diverse etiologies including ischemia, hypertension, obesity, and aging. Recently,
wtTTR amyloidosis has been considered an important but under-recognized contributor to age-related HFpEF. Mohammed, et al.15 examined amyloid deposits in autopsy specimens of the LV and demonstrated the high prevalence of wtTTR amyloidosis in patients with HFpEF. Additionally, a Spanish study comprising patients with both HFpEF and LVH (≥12 mm) demonstrated wtTTR amyloidosis in 13% of these patients.15 In the present study, about 0.4% of patients older than 70 years showed a positive DPD scan, whereas 98% of patients (216/221) demonstrated diastolic dysfunction on transthoracic echocardiography (TTE). Patients with positive DPD scans included in our study showed expected E’ velocity and pulmonary artery systolic pressure for their age, suggesting that patients with wtTTR amyloidosis could show diastolic dysfunction in a manner expected for their age. The complaint of dyspnea is quite subjective; moreover, its development is usually gradually progressive in nature. It is quite likely that quite a number of patients included in our study might complain of dyspnea later on and might be classified as patients with HFpEF. Therefore, it is conceivable that there is a wide etiologic overlap between the group included in this study, and the group of elderly patients with HFpEF showing high incidence of wtTTR amyloidosis. Additional studies are needed to determine the true incidence of wtTTR amyloidosis in patients with HFpEF.

Patients with a positive DPD scan included in our study showed expected E’ velocity and pulmonary artery systolic pressure for their age, indicating that, in asymptomatic patients, severity of diastolic dysfunction cannot be used to indicate the possibility of wtTTR amyloidosis.

Limitations: Even with the high sensitivity and specificity of the DPD scan, the prevalence of wtTTR amyloidosis could be underestimated. However, low sensitivity issue of DPD scan which might result from the amount of amyloid deposit required for a positive DPD scan, may better represent clinically significant amyloid deposits compared to the histologic diagnosis of cardiac amyloidosis.

This was a retrospective study; thus, we could not provide the symptomatic status of the patients. For the same reason, echocardiography was performed in a relatively small number.

Conclusion

The prevalence of wtTTR amyloidosis in the elderly population, estimated by a positive DPD scan, was much lower than that recently suggested. Therefore, it is likely that wtTTR amyloidosis might not be a prevalent but unrecognized cause for age-related diastolic dysfunction, nor the etiology of HFpEF in the elderly contrary to what has been suggested in recent studies.

Disclosures

Conflicts of interest: The authors have no conflict of interests relevant to this article.

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