RESEARCH ARTICLE

Suspected transthyretin cardiac amyloidosis by cardiac scintigraphy in heart failure with preserved ejection fraction, left ventricular hypertrophy and red flag manifestations

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ABSTRACT

Background

Transthyretin Cardiac Amyloidosis (ATTR) is a type of restrictive cardiomyopathy, which typically manifests as Heart Failure with Preserved Ejection Fraction (HFpEF).

The presence of unexplained left ventricular hypertrophy (LVH) associated with HF and red flag manifestations could increase the diagnostic probability. However, the diagnostic prevalence of this triad by cardiac scintigraphy remains uncertain.

Methods

From August 1st to December 31st, 2021, 22 consecutive patients diagnosed with a HF (ejection fraction more than 40%), LVH with unexplained etiology and at least one red flag clinical manifestation, underwent pyrophosphate scintigraphy (99mTc-PYP). The patients were divided into two groups: "Positive" and "Negative" (as defined by grade 2 or 3 uptake). Multiple logistic models were made with variable 99mTC-PYP and explanatory variables.

Results

Among 22 patients, 15 had a positive 99mTc-PYP study for ATTR. The prevalence of ATTR using the triad of HFpEF, unexplained LVH and at least one red flag was 68% (CI 95%; 45-86%). Patients with 99mTc-PYP positive tended to be male, older, and with an aortic mean gradient and interventricular septum higher, as compared to the group with a negative study. The most frequent red flag clinical manifestations were proteinuria (55%) and pseudoinfarction pattern (55%). The presence of 2 or more red flags could increase the diagnostic probability of the test (OR 1.6 (CI95% 0.52-4.89).

Conclusions

The diagnostic probability of ATTR by 99mTc-PYP scan could increased when a clinical manifestation of a red flag was added to the suspected diagnosis of heart failure and left ventricular hypertrophy. The use of non-invasive techniques allows early identification and treatment of this underdiagnosed disease.

Keywords: Amyloidosis; Heart Failure; Restrictive Cardiomyopathy.

1. INTRODUCTION

Cardiac Amyloidosis (CA) is a type of restrictive cardiomyopathy, in which the infiltration of amyloid fibers into the myocardial tissue produces progressive ventricular stiffness, wall thickening and diastolic dysfunction due to restrictive physiology, which typically manifests as Heart Failure with Preserved Ejection Fraction (HFpEF).[1,2,3]

More than 95% are caused by transthyretin amyloidosis (ATTR) or light chain amyloidosis (LA). In the case of ATTR, the TTR protein can dissociate into monomers and oligomers, and then be deposited as amyloid fibers; in a natural way (ATTRwt or "wild type") or genetic (ATTRm or "Mutant").[4]

CA should be suspected when the patient presents symptoms and signs of HF with unexplained left ventricular hypertrophy (LVH) (> 12 mm) and 1 or more clinical manifestations. Several research studies have established red flags signs and symptoms, and recognizing them continues to be the main clinical challenge.[5,6]

Red flag signs and symptoms, elevated biomarkers, and grade 2-3 uptake with pyrophosphate scintigraphy (99mTc-PYP),

excluding a monoclonal protein in serum and urine that could cause AL, confers a 100% positive predictive value for the diagnosis of ATTR. The use of non-invasive techniques allows the early identification and treatment of this disease, the incidence and prevalence of which are still uncertain.[5,6]

We conducted a quality improvement project (QIP) to optimize the patient care for ATTR, with the objective of determining the prevalence of ATTR in patients from northern Ontario, presenting the triad composed of HFpEF, unexplained LVH, and at least red flag clinical manifestation. Prevalence was defined by screening with 99mTc-PYP.

2. METHODS

2.1 Study setting

This was a prospective QIP, from August 1st to December 31st, 2021, conducted at the Heart Failure Disease Management Program (HFDMP), in Health Sciences North (HSN), Sudbury, Canada.

Patients attending the HFDMP with a previous validated diagnosis of HF, with EF more than 40% and a LV thickness greater than 12 mm of unexplained etiology with 1 or more red flag clinical manifestation were included: over 65 years old; aortic stenosis (AS); autonomic dysfunction, sensorial compromise; peripheral polyneuropathy; proteinuria; periorbital hematomas; bilateral carpal tunnel syndrome; biceps tendon rupture; low voltage; pseudoinfarction pattern; AV conduction disorders; family history of amyloidosis. The objective of this QIP was to optimize the patient care for ATTR patients at HSN.

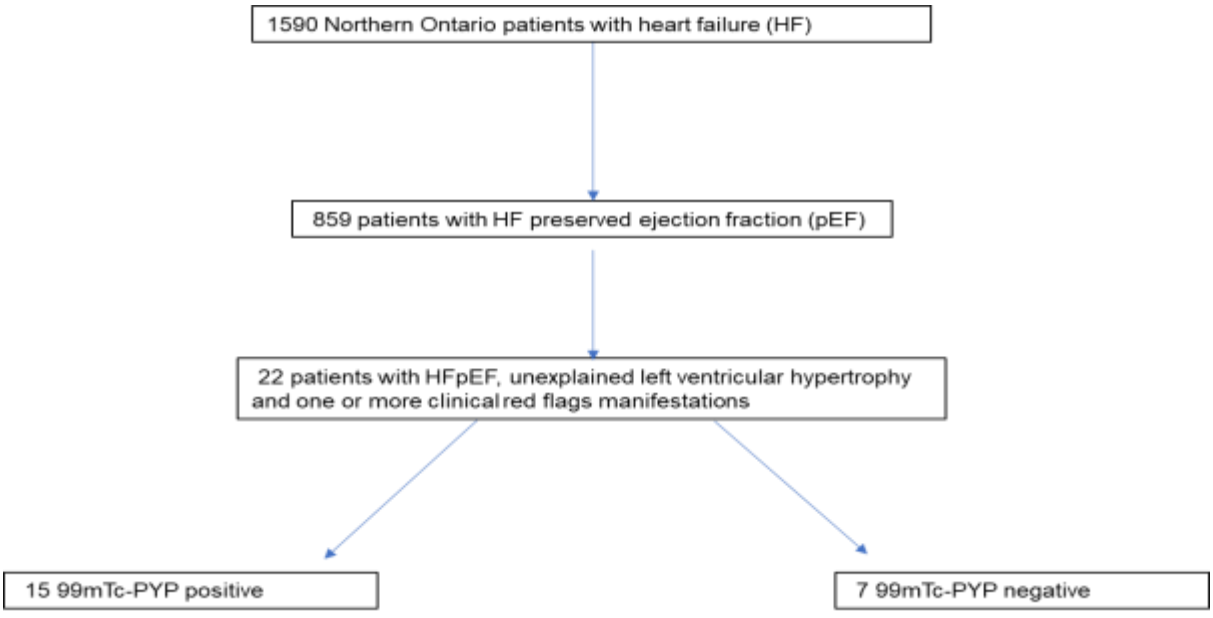
2.2 Study protocol

Patients with EF less than 40% or HF and LVH of known etiology were excluded.

The rest of the patients formed the cohort (Figure 1) in which the prevalence of ATTR was evaluated using 99mTc-PYP.

Clinical, echocardiographic, electrocardiographic, laboratory and scintigraphy data were collected. The positive results through the exploration with 99mTc-PYP, were subjected to salivary gland biopsy and saliva genetic test to differentiate mATTR vs wtATTR. The study was approved by the Hospital's Institutional Review Board.

Figure 1. Community cohort



2.3 Data management

All data obtained in this study were entered into Microsoft Excel spreadsheets. Study participants were divided into positive or negative 99mTc-PYP scans. Positive 99mTc-PYP scan included those with an uptake grade 2 or 3 based on Perugini's score.

2.4 Statistical analysis

The patients were divided into positive and negative 99mTc-PYP, and analyses were performed accordingly. Descriptive statistics were used to analyze differences in baseline and clinical characteristics, using Fisher's exact tests for categorical variables, and the t-test for continuous variables, where appropriate. Test selection was based on data distribution and normalcy.

Odds ratio (OR) and 95% confidence interval (CI) were calculated to test the univariate associations between positive 99mTc-PYP scans and red flag manifestations.

The red flags and the presence of symptoms were grouped into 2 individual variables and a logistic regression model was performed according to the result of the 99Tc-PYP scan. The variable red flag was categorized as 0 to 2 present and more than 2 present.

Statistical analyses were performed using EPI info Statistics for Windows version 21.

3. RESULTS

A total of 22 Northwest Ontario residents with HFpEF, LVH of unknown etiology and at least 1 red flag were recruited, including 15 (68%) with a positive scan; and 7 (32%) with a negative 99mTc-PYP scan (Table 1).

Table 1. Baseline and clinical characteristics

Characteristics	**All n = 22**	**PYP positive n = 15**	**PYP negative n = 7**	**p-value**
Baseline				
Age, mean ± SD	74.9 ±12.9	77.5 ± 9.06	69 ±14.2	0.04
Male, n (%)	14 (64%)	10 (66.6%)	4 (57%)	0,51
White race, n (%)	21 (95%)	14 (93.3%)	5 (100%)	0.75
Angina, n (%)	6 (27%)	3 (20%)	3 (42%)	0,26
Stroke, n (%)	3 (14%)	1 (7%)	2 (29%)	0,22
Atrial fibrillation, n (%)	14 (64%)	9 (60%)	5 (71%)	0.48
LBBB, n (%)	1 (5%)	1 (7%)	0 (0%)	0.68
Pacemaker/ICD, n (%)	2 (9%)	2 (13.3%)	0 (0%)	0,45
IVS mm, mean ± SD	13.77 ± 2.02	14.33 ± 2.19	12.57 ± 0.78	0.01
EF%, mean ± SD	56.59 ± 7.42	55.93 ± 7.32	58 ± 8.02	0.55
Aortic Vel. max (m/seg), mean ± SD	1.62 ± 0.81	1.79 ± 0.89	1.26 ± 0.51	0,07

Mean gradient (mmHg), mean ± SD	8.59 ± 6.68	10.2 ± 7.42	5.14 ± 2.67	0.01
Creatinine (umol/L), mean ± SD	193.59 ± 196.43	145 ± 71,9	297.57 ± 323.22	0.12
Urea (mmol/L), mean ± SD	18.43 ± 10.01	15.8 ± 6.19	26.25 ± 15.9	0.028
Bilirubin (umol/L), mean ± SD	13.28 ± 7.88	12 ± 5.44	15.8 ± 11.46	0.03
NT-proBNP (ng/L), mean ± SD	4508.95 ± 5366.91	3651.26 ± 4478.67	7725.25 ± 7857.80	0.18
Troponin (ug/L), mean ± SD	0.10 ± 0.25	0.13 ± 0.30	0.04 ± 0.08	0.08
Kappa (mg/L), mean ± SD	50.87 ± 52.82	31.10 ± 13.79	90.40 ± 33.62	0.0001
Lambda (mg/L), mean ± SD	35.53 ± 33.62	26 ± 12.73	54.60 ± 53.94	0.0008

Abbreviations. LA, light chain amyloidosis; EF, ejection fraction; ICD, implantable cardioverter defibrillator; IVS, interventricular septum; LBBB, left bundle branch block; IQR, interquartile range; PYP, pyrophosphate scintigraphy; SD, standard deviation; TAVI, transcatheter aortic valve implantation

3.1 Baseline characteristics

As shown in Table 1, the mean age of the total cohort was 74.9 ±12.9 years, 64% were male. Patients with an abnormal 99mTc-PYP were older, more likely to have left bundle branch block (LBBB), lower incidence of kidney failure and lower levels of light chains, as compared to patients with negative 99mTc-PYP. Although there was no difference between LVEF, those with a positive 99mTc-PYP presented higher aortic mean gradient (10.2 ± 7.42 vs. 5.14 ± 2.67; p-value: 0.01) and greater thickening of the LV wall as compared to the negative 99mTc-PYP (14.33 ± 2.19 vs 12.57 ± 0.79; p-value: 0.01).

3.2 Red flag manifestations results

The most frequent red flags were proteinuria (55%), electrocardiographic pattern of pseudoinfarction (55%) and low voltage (14%).

As shown in Table 2, patients with a positive 99mTc-PYP tended to have a higher incidence of sick sinus syndrome, neuropathy, bilateral carpal tunnel and gastrointestinal bleeding.

The prevalence of 99mTc-PYP positive was higher in men (67%) than in women, although it was not statistically significant (p-value 0,51) and in older patients (77.5 ± 9.06 years vs. 65 ±19.9 years; p-value:0.04).

Table 2. Red flag manifestations of the cohort

Red flag manifestations	All n = 22	PYP positive n = 15	PYP negative n = 7	p-value
Over than 65, n (%) years	19 (87%)	14 (93%)	5 (71%)	0.22
Over than 75 years, n (%)	14 (64%)	9 (60%)	4 (57%)	0.62
Over than 85 years, n (%)	5 (23%)	4 (27%)	1 (15%)	0.47
Stenosis Aortic, n (%)	1 (5%)	1 (7%)	0 (0%)	0.68
AV block, n (%)	1 (5%)	1 (7%)	0 (0%)	0.68
Sick sinus, n (%)	1 (5%)	1 (7%)	0 (0%)	0,68
Low voltage, n (%)	3 (14%)	1 (7%)	1 (29%)	0.22
Seudoinfartion pattern, n (%)	12 (55%)	7 (47%)	5 (71%)	0.26
Proteinuria, n (%)	12 (55%)	8 (53.3%)	3 (60%)	0.60
Neuropathy, n (%)	1 (5%)	1 (6.67%)	0 (0%)	0.75
Bilateral tunnel carpal syndrome, n (%)	1 (5%)	1 (6.67%)	0 (0%)	0.75
GI bleeding, n (%)	2 (9%)	2 (13.3%)	0 (0%)	0.55
Familiar history of ATTR, n (%)	0 (0%)			
Light chains ratio <1.65, n (%)	9 (45%)	6 (40%)	3 (60%)	0.39
LA, n (%)	2 (9%)	0 (0%)	2 (29%)	0.09
Salivary biopsy, n (%) positive for amyloid	4 (18%)	2 (13%)	2 (29%)	0.37
Genetic test positive for ATTR, n (%)	0 (0%)			

Abbreviations. AS, aortic stenosis; ATTR; transthyretin amyloidosis; AV, atrioventricular; GI, gastrointestinal bleeding; LA; light chain amyloidosis; PYP, pyrophosphate scintigraphy.

The diagnosis of ATTR was confirmed by salivary gland biopsy in 25% of the cases and genetic testing was negative for TTR mutation in 100%.

2 patients (40%) with 99mTc-PYP grade 1, salivary biopsy showed LA, and this association was statistically significant (p-value 0.04).

The prevalence of ATTR by 99mTc-PYP screening in patients with the triad was 68% (CI 95%; 45-86%), and increased markedly with age as compared with 99mTc-PYP negative, from 80% in patients aged 65 years

to 67% in patients aged 75 years and 80% in patients aged 85 or older.

The presence of 2 or more red flags, any of the previously mentioned symptoms, a kappa/lambda ratio <1.65, or age over 65 years could increase the diagnostic probability of the test. (Table 3)

Table 3. Multiple logistic model with 99mTc-PYP and variables

Variable	OR (CI 95%)
2 or more red flags	1.6 (0-52-4.89)
Clinical manifestations	1.25 (0.33-4.65)
Light chains ratio <1.65	3.5 (0.73-16.85)
Aged over 65 years old	2.8 (1.01-7.77)

Abbreviations. CI, confidence interval; OR, odds ratio.

4. DISCUSSION

Amyloidosis refers to the process of abnormal proteins folding due to various factors over the patient's lifetime, or due to genetic inheritance. There are currently 26 identified proteins that are affected by this process and leading to various disease manifestations. The resultant abnormal protein fibers are deposited in the interstitial spaces, of in this case, the myocytes in the heart, but also in other tissues.

CA should be suspected when the patient presents the triad composed of HFpEF, LVH of unknown etiology, and at least one red flag manifestation.[6]

The term hypertrophy is a misnomer since it is not the myocytes that are hypertrophied, but the expansion of the interstitial space. The fact that the myocytes initially can function normally may explain why these patients initially have relatively maintained LVEF.

Clinical signs of CA with echocardiography, cardiac magnetic resonance, elevated biomarkers, and grade 2-3 uptake with 99mTc-PYP in scintigraphy, with the exclusion of a monoclonal protein that could cause AL by the light chain test in serum and urine, confer a positive predictive value of 100% for the diagnosis of ATTR. In these cases, biopsy is not required, and genetic testing should be performed to distinguish a “hereditary” from “wild” variant.[6,7]

ATTR is underdiagnosed and it is important to connect early associated signs and symptoms or so-called red flags to identify the disease at the earliest time given these patients can now be offered effective therapies.[6]

The number of patients diagnosed with ATTR has increased over the years and it has been considered that it may be more frequent than AL, with a prevalence of 20% in patients with HF and an increase in the thickness of the myocardial wall of more than 12 mm.[7]

TTR deposits have been identified in 25% of autopsies in patients older than 80 years; by noninvasive imaging methods, it is estimated that ATTR represents 13% of patients with HFpEF and 16% of those who undergo transcutaneous aortic valve replacement

(TAVI) for severe aortic stenosis (AS) with low-flow, low-gradient and pFE (paradoxical).[8]

Abou Ezzeddine et al recently detected a 6.3% prevalence of this pathology when systematic screening with 99mTc-PYP is performed.[9]

This study demonstrated a 68% prevalence of ATTR when a red flag manifestation is added to the suspected diagnosis, such as sick sinus syndrome, neuropathy, bilateral carpal tunnel and gastrointestinal bleeding.

The presence of 2 or more red flags, clinical manifestations as angina or stroke, a light chains ratio <1.65 and age over 65 years increased the diagnostic probability of the test, and these initial results could be useful when examining patients for ATTR.

Although the reported sensitivity of salivary gland biopsy is close to 91%, in this study the diagnostic yield was much lower (25%). This may be due to the early diagnosis of the disease with 99mTc-PYP, and the lack of systemic involvement.[10]

The initial results could be useful to avoid unnecessary studies and also detect patients at an earlier stage of disease and thus increasing the possibility that the therapies will be more effective.

With the 99mTc-PYP imaging it is becoming clear that the disease is more prevalent in the population than initially recognized. The challenge for the family physicians and cardiologist is to recognize the various features of the cardiac presentation and the importance of red flags findings to make the diagnosis at the earliest possible time.

5. LIMITATIONS

This is a prospective, single-center QIP and not a randomized trial, and such is subjected to associated confounding factors.

The QI was conducted with a small cohort and high prevalence of caucasian participants, and does not reflect the demographic characteristics of the world population.

The low positivity of the salivary gland biopsy should be confirmed by endomyocardial biopsy.

6. CONCLUSIONS

Cardiac amyloidosis is an entity that is being diagnosed with increasing frequency. Recognizing the red flags continues to be the main clinical challenge, and can be the first step towards a definitive diagnosis.

The diagnostic probability of ATTR could be higher when red flags manifestations are added to the initial suspicion of heart failure with preserved ejection fraction and unexplained left ventricular hypertrophy.

A systematic screening through the use of non-invasive techniques such as 99mTc-PYP, allows the identification and early treatment of this disease, whose incidence and prevalence are increasing.

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