Usefulness of $^{99}$mTc-HDP scintigraphy in the diagnosis of suspected cardiac amyloidosis revealed by heart failure: A case report of an amyloidogenic transthyretin mutation

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ABSTRACT

Abstract is not required for Clinical Images
Usefulness of $^{99m}$Tc-HDP scintigraphy in the diagnosis of suspected cardiac amyloidosis revealed by heart failure: A case report of an amyloidogenic transthyretin mutation

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CASE REPORT

A 54-years-old Guadeloupean patient known to have hypertrophic cardiomyopathy with severe left ventricular systolic dysfunction was hospitalized for cardiogenic shock. Ventricular arrhythmia lead to an implantable cardioverter-defibrillator (ICD). While most investigations proved to be unsuccessful, cardiological assessment showed: a micro-voltage on electrocardiogram (ECG); an increased level of N-terminal form of B-type natriuretic peptide (nT-pro-BNP) to 12000 ng/L; a restrictive infiltrative cardiomyopathy with concentric and homogeneous left ventricular hypertrophy and a severe biventricular dysfunction on echocardiography (Figure 1). A cardiac single photon emission computed tomography (SPECT), performed three hours after the intravenous injection of 600 MBq of $^{99m}$-technetium oxidronate ($^{99m}$Tc-HDP) revealed abnormal myocardial uptake (Figure 2A–B) that was prominent on apical and anteroapical walls and moderate on antero-medial-septal wall (Figure 2C). In this context, the scintigraphy was highly suggestive of cardiac amyloidosis. This diagnostic was confirmed thereafter by myocardial biopsy that showed extracellular amyloid deposits (Figure 3). Antibody anti-transthyretin revealed by immunohistochemical analysis of amyloidosis was in favor of a transthyretin form. Genetic sampling showed homozygous missense mutation valine to isoleucine substitution at position 122 (V122I) of TTR gene.
Amyloidosis is characterized by extracellular tissue deposition in vital organs of misfolded proteins [1, 2]. Among systemic amyloidosis, immunoglobulin light-chain amyloid (AL-form) and transthyretin amyloid (ATTR-form) are known to infiltrate the heart leading to congestive heart failure, atrial fibrillation and conduction abnormalities [2, 3]. The TTR-form of cardiac amyloidosis, an underdiagnosed cause of heart failure, is slowly progressive and clinically well tolerated while AL-form often lead to rapidly progressive cardiac dysfunction. An early recognition and accurate classification of both entities, potentially fatal, is necessary because treatment depends on amyloidosis type. The ATTR-form may be either familial (variant TTR) caused by a mutation, or sporadic (aged-related) due to misaggregation of a wild-type transthyretin [2]. TTR is a transport protein primarily expressed by the liver and circulates as homotetramer; under genetic mutation or aging, tetramers dissociate to monomers leading to amyloid fibrils [2]. Aggregate autopsy data show presence of wild-type TTR in 25–30% of hearts, leading to cardiac dysfunction in a smaller but significant elderly population [2, 4]. As for variant TTR more than 80 mutations have been described [1]. V122I TTR variant is one of the most widespread with a population prevalence of 4% in Afro-Caribbeans [2, 4]. Its diagnosis has to be confirmed by the immunohistochemical demonstration of amyloidogenic TTR-form on a biopsy specimen and by the presence of an ATTR mutation on protein/DNA analysis [2–4]. However myocardial biopsy is not often performed in practice because it is invasive, results are late with the possibility of false-negatives. Non-invasive diagnostic approaches such as ECG and echocardiography have low specificity and sensitivity, respectively [2]. Cardiac magnetic resonance (CMR) is hampered by limited availability and inability to image patients with pacemaker or ICD. This modality is able to identify amyloid infiltration by late gadolinium enhancement imaging (with a sensitivity and specificity of 90%), keeping in mind the potential risk of nephrogenic systemic fibrosis in these patients with frequent chronic kidney disease [2]. To note, radionuclide imaging shows a potential interest for identification cardiac amyloid deposits. With SPECT, a myocardial uptake of 99m-technetium diphosphono-propanodicarboxylic acid (99mTc-DPD) is able to differentiate mutation carriers from the AL-form [1], likely due to higher concentrations of calcium-containing products in TTR amyloid [5]. Quantification of amyloid burden by scintigraphy could predict cardiac events and thus have an impact on determining therapeutic strategies. 99mTc-DPD cardiac retention can be scored as follow:

- **Grade 0** for no visible myocardial uptake in both the delayed planar or cardiac SPECT;
- **Grade 1** for cardiac uptake on SPECT only or cardiac uptake of less intensity than the accompanying normal bone distribution;
- **Grade 2** for moderate cardiac uptake with some attenuation of bone signal
- **Grade 3** for strong cardiac uptake with little or no bone uptake [6]. The possibility of a prognostic assessment by quantification allows to follow-up the course of the disease while new specific therapies for TTR amyloidosis are emerging (such as TTR stabilizers and small RNA silencing molecules). 18fluorine-florbetapir positron emission tomography (18F-Florbetapir PET) approved for beta amyloid plaque in the brain, was investigated in cardiac amyloidosis and showed high myocardial radiotracer uptake and late retention of 18F-Florbetapir in amyloid subjects suggesting a correlation with amyloid protein. However, its value in the diagnosis of cardiac amyloidosis remains to be confirmed [7]. Another interesting SPECT tracer is 123iodine-metaiodobenzylguanidine (123I-MIBG) for imaging of myocardial innervation. The localization of MIBG relates to the presence of sympathetic nerves. Myocardial defects in MIBG activity seems to correlate...
with impaired cardiac sympathetic nerve endings due to amyloid deposits and can be identified very early in cardiac amyloidosis. Furthermore, the clinical severity of disease correlates with a decrease in MIBG uptake [1].

CONCLUSION

In conclusion ⁹⁹mTc-HDP or ⁹⁹mTc-DPD scintigraphy appears to be a major examination to establish the aetiology of cardiac amyloidosis with a high specificity, especially as age-related ATTR could become the most common form of this disease in the future. This could facilitate the ATTR specific care (genetic counselling, preventing measures and interference with medications). Furthermore with a simple and non-invasive method, whole-body tracer retention and specifically myocardial tracer retention correlated with disease severity could be used for prognostic assessment.

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**Author Contributions**

Geraldine Celine Bera – Substantial contributions to conception and design, Analysis and interpretation of data, Drafting the article, Final approval of the version to be published

Lavinia Vija – Substantial contributions to conception and design, Revising it critically for important intellectual content, Final approval of the version to be published

Pierre Jean Fouret – Acquisition of data, Analysis and interpretation of data, Revising it critically for important intellectual content, Final approval of the version to be published

Nathanaëlle Yeni – Analysis and interpretation of data, Revising it critically for important intellectual content, Final approval of the version to be published

**Guarantor**

The corresponding author is the guarantor of submission.

**Conflict of Interest**

Authors declare no conflict of interest.

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