SPECT and PET in Sympathetic Innervation

Noordzij, Walter

CHAPTER 3

Clinical use of differential nuclear medicine modalities in patients with ATTR amyloidosis

Walter Noordzij[1], Andor W.J.M. Glaudemans[1], Rudi A.J.O. Dierckx[1], Riemer H.J.A. Slart[1], Bouke P.C. Hazenberg[2]

[1] Department of Nuclear Medicine and Molecular Imaging, [2] Department of Rheumatology and Clinical Immunology, University of Groningen, University Medical Center Groningen, The Netherlands

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ABSTRACT

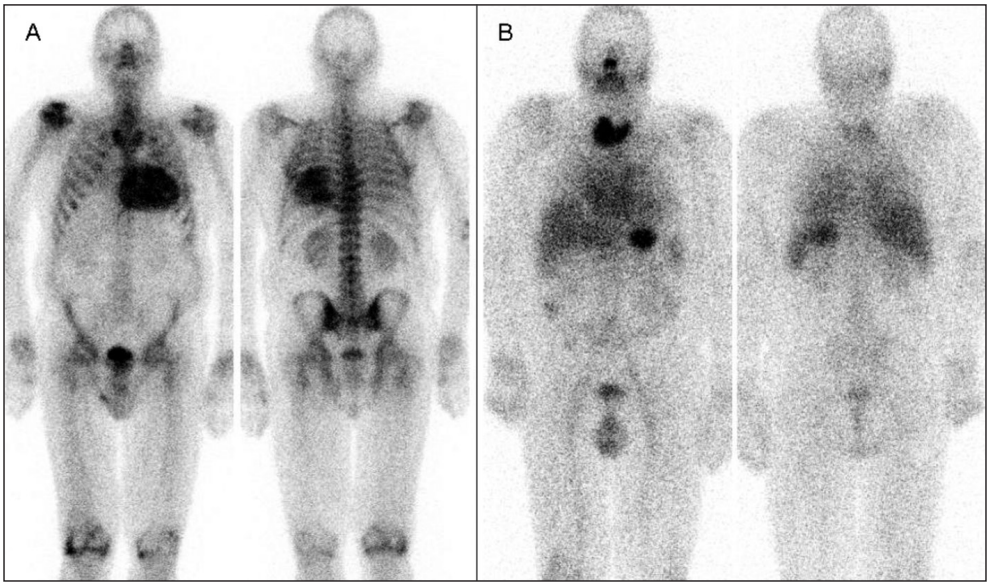
Histological proof remains the gold standard for the diagnosis of amyloidosis. Nuclear medicine imaging techniques are able to determine the amyloid load in the body. Currently, the best imaging modality is ^{123}I-SAP scintigraphy. This modality has high sensitivity for detecting amyloid deposits in all amyloid subtypes. Involvement of liver and spleen can be visualized before clinical signs are present. The addition of single photon emission computed tomography improves the differentiation of overlying organs. However, ^{123}I-SAP is not FDA approved. Its availability is limited to two centres in Europe. Furthermore, it is not suitable for imaging cardiac involvement of amyloidosis, due to movement, blood-pool content and lack of fenestrated endothelial in the myocardium. Phosphate derivates labelled with ^{99}Tc, are able to detect calcium compounds in cardiac amyloidosis. Finally, ^{123}I-MIBG, an analogue of norepinephrine, can detect cardiac sympathetic innervation abnormalities as a consequence of amyloid deposits. Both these last techniques seem to be able to detect cardiac involvement before echocardiographic parameters are present. We illustrate the clinical use of these modalities with two patients with ATTR type amyloidosis.

Histological proof from biopsied tissue, such as adipose tissue, is the gold standard for the diagnosis of amyloidosis (1). However, this invasive procedure is subject to sampling errors. Furthermore, although it may provide information on the presence or absence of systemic amyloidosis, it does not inform about the extent of involvement of different organs. Therefore, there is a need for adequate imaging techniques to determine the amyloid load in the body.

Mutations in the normal transport protein transthyretin (TTR) result in misfolding of the protein, making the protein amyloidogenic and an important cause of ATTR amyloidosis. These TTR mutations are inherited in an autosomal-dominant way and this type of amyloidosis is characterized by peripheral and autonomic neuropathy and/or cardiomyopathy. However, in elderly patients, normal TTR can also become amyloidogenic, leading to "wild-type" ATTR amyloidosis that is characterized by a slowly progressive cardiomyopathy (2). In this report, we provide an overview of available nuclear medicine imaging modalities, as illustrated by two cases suffering from ATTR amyloidosis.

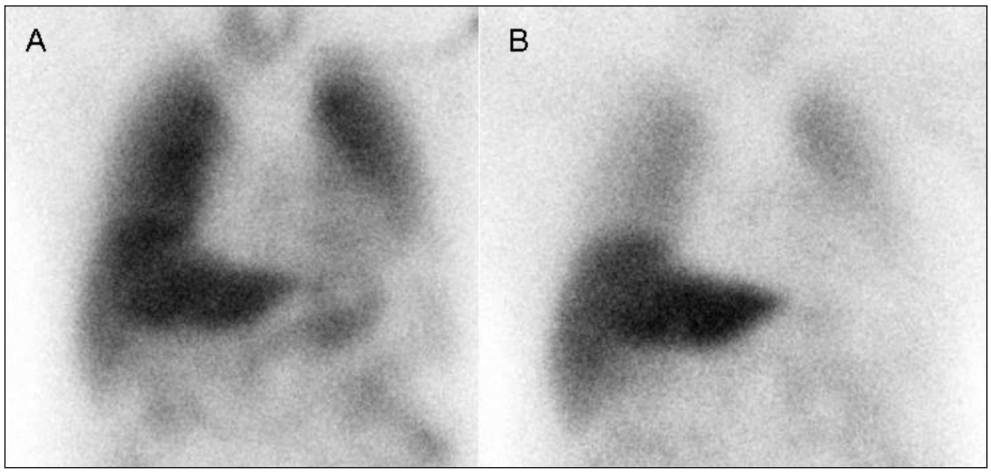
Patient A is a male of 67 years of age, who was referred to the internal medicine outpatient clinic because of wild-type ATTR amyloidosis with indolent progressive cardiomyopathy. Complaints of fatigue, ankle oedema and dyspnoea started 5 years earlier, for which he was referred to a cardiologist. An echocardiogram at that time did not provide any clue for cardiac amyloidosis. The coronary angiogram showed normal coronary anatomy, however pulmonary artery pressures were elevated as well as end diastolic pressure in the left ventricle (LV), indicating diastolic heart failure. He was treated with diuretics, with initially good effect. During the next two years his complaints of exercise intolerance aggravated again. A second echocardiogram showed thickened LV walls (septum 13 mm, posterior wall 17 mm) and highly refractile echoes, typical signs of cardiac amyloidosis. The myocardial biopsy showed extensive interstitial amyloid deposition, with positive immunohistochemical stain for transthyretin. Additional analysis of the TTR gene did not show any mutation, thereby confirming the clinical diagnosis of wild-type ATTR amyloidosis. Iodine-123 labelled Serum amyloid P component ([^{123}I]-SAP) scintigraphy revealed no specific uptake in liver, spleen, kidneys and adrenal glands, whereas some uptake was seen in shoulders and wrists, and the tissue retention of SAP was elevated (55%). Conventional bone scanning with technetium-99m labelled hydroxymethane diphosphonate ([^{99m}Tc]-HDP) showed uptake in the large joints, but also in the heart, in concordance with cardiac ATTR amyloidosis (Figure 1). Also, iodine-123 labelled metai-odobenzylguanidine ([^{123}I]-MIBG) scanning was performed, which showed a late heart-to-mediastinum (HMR) ratio of 1.57 and a high-washout rate (>20%), indicating cardiac sympathetic denervation.

Figure 1
Anterior and posterior views of a [^{99m}Tc]-HDP scintigraphy (**A**) and a [^{123}I]-SAP in patient A (**B**). Myocardial tracer accumulation on the bone scintigraphy is not present on the [^{123}I]-SAP scan. Both modalities show uptake in the major joints. Normal [^{123}I]-SAP uptake in the thyroid gland and stomach.



Patient B is a 66-year-old female, who was also referred to the internal medicine outpatient clinic because of signs of amyloidosis on an echocardiogram. This patient was analyzed on the cardiology department because of sudden dyspnoea, which started one year earlier. She suffered from exercise intolerance, however she had no ankle oedema. Because of hypertension she was treated with diuretics and angiotensin converting enzyme inhibitors, which relieved her complaints. Her medical history revealed hypothyroidism, arthropathy of the right shoulder and carpal tunnel syndrome on both sides. Laboratory results showed a slightly elevated level of kappa free light chains (35 mg/L, reference value 2-20 mg/L) and a highly elevated N-terminal pro brain natriuretic peptide (NT pro-BNP, 2291 ng/L, reference value < 100 ng/L), TTR gene analysis showed a homozygous TTR-Val122Ile mutation. Despite the initial clinical suspicion on AL amyloidosis, because of arthropathy and cardiomyopathy, the final diagnosis appeared to be ATTR amyloidosis. [^{123}I]-SAP scintigraphy was performed and showed specific uptake in the spleen, as well as in the shoulders and wrists. Also the tissue retention of SAP was elevated (60%). Conventional bone scanning revealed high tracer uptake in the shoulders and wrists as well, with high accumulation in the myocardium. Additional [^{123}I]-MIBG scanning showed signs of cardiac sympathetic denervation, with late HMR 1.13 and washout rate 28% (Figure 2).

Figure 2
Anterior views of the thorax of patient B, 15 min (**A**) and 4 h (**B**) after administration of [^{123}I]-MIBG. The low uptake in the myocardium, as well as the decrease in uptake over time, indicate cardiac sympathetic denervation.



Currently, the best modality for the extent and distribution of amyloid deposition in all types of amyloidosis is the [^{123}I]-SAP-scintigraphy (3). However, its availability is limited since it has not been approved by the US Food and Drug Administration due to the human plasma source of this protein. In fact, it is used only in the University College London (UK) and the University Medical Center Groningen (the Netherlands). Despite the fact that SAP is also present in healthy individuals, mainly circulating in the plasma compartment, its concentration is much higher in amyloid depositions of patients with systemic amyloidosis. When labelled to iodine-123, it makes [^{123}I]-SAP very suitable for amyloid imaging. Clinical studies have proven high sensitivity in determining sites of amyloid deposition for all amyloid subtypes (4). Involvement of either the liver or the spleen can be visualized even before clinical signs are present. Furthermore, serial scanning can provide evidence of progression and regression (5). The [^{123}I]-SAP images are analyzed in a semiquantitative way, by comparing each organ directly or indirectly to the normal blood-pool distribution. Organ involvement in graded on a 4-point scale [6]. In a healthy individual, there is no organ deposition and the tracer is confined to the blood-pool and major blood organs. Therefore, any uptake in for example the joints which is higher than the surrounding tissue (as in both patients), is considered "specific" for amyloid deposits.

The tissue retention is determined using urinary and blood samples which are collected the day after administration of [^{123}I]-SAP. The value of the tissue retention gives an impression of the total body burden and may sometimes help to diagnose amyloidosis. However, it does not reliably predict clinical stage or prognosis in individual patients (6).

Often, uptake in smaller organs such as the adrenal glands is difficult to assess, due to image quality as well as to high uptake in neighbouring organs (liver and spleen). Complementary single photon emission computed tomography (SPECT), in which a three-dimensional reconstruction is performed of the abdomen, is able to identify amyloid deposits in individual organs which are projected over each other on the planar images. The introduction of hybrid camera systems combines SPECT with computed tomography (SPECT/CT) of the abdomen and makes exact localization of pathological uptake in specific organs easier.

Unfortunately, this modality is not suitable for imaging cardiac amyloidosis, due to movement, blood-pool content and lack of fenestrated endothelium in the myocardium (6). Other techniques are available for this indication. One of those techniques is the use of [^{99m}Tc] labelled phosphate derivates (7). Several [^{99m}Tc] labelled radiopharmaceuticals are available for imaging calcium compounds in amyloid deposits, with pyrophosphate ([^{99m}Tc]-PYP), methylene diphosphonate ([^{99m}Tc]-MDP) and 3,3-diphosphono-1,2-propanodicarboxylic acid ([^{99m}Tc]-DPD) most frequently reported (8). Interestingly, one report suggests that [^{99m}Tc] -DPD is able to differentiate between AL and ATTR amyloidosis (9). The myocardial uptake was significantly higher in patients with ATTR amyloidosis, with the AL patients showing no uptake at all. Those patients also underwent bone scanning using [^{99m}Tc]-MDP, showing no myocardial uptake at all. This last finding is actually in disconcordance with our two patients, since [^{99m}Tc]-MDP and [^{99m}Tc]-HDP are very closely related diphosphonates. However, myocardial uptake on bone scintigraphy allows early diagnosis of amyloidotic cardiomyopathy, even before abnormalities on echocardiography are present (10).

Another technique for imaging cardiac amyloidosis, or actually the consequences of amyloid deposits on the sympathetic nerve system, is the use of [^{123}I]-MIBG (11). This tracer is widely accepted for diagnosing cardiac sympathetic denervation. [^{123}I]-MIBG is an analogue of the false neurotransmitter guanethidine, and therefore of norepinephrine (NE). Like NE, it is taken up by the uptake-1 mechanism and stored in sympathetic nerve endings. In contrast to NE, [^{123}I]-MIBG is not further metabolized by enzymes. It is retained in vesicles and supposed to be washed out in the situation of impaired sympathetic tone only. Another parameter, besides the washout, which is used to define the uptake in the myocardium, is the HMR on early (15-min post-tracer injection [pi]) and late (4-h pi) images.

Nowadays, a [^{123}I]-MIBG scan using late HMR and washout rates is a well-established modality for the evaluation of cardiac sympathetic tone, especially in patients with ATTR amyloidosis. Not only do these patients show lower HMR and higher washout rates than other amyloid type patients and healthy controls, the use of [^{123}I]-MIBG is also able to identify myocardial involvement before echocardiographic parameters are present (12). Furthermore, it may have a role in the indirect measurement of amyloid myocardial infiltration (7).

This report mainly focuses on the use of conventional nuclear medicine modalities, including the use of hybrid SPECT/CT systems. Positron emission tomography (PET) is another major modality within nuclear medicine. The role of

PET radiopharmaceuticals, especially [^{18}F]-FDG, in systemic amyloidosis is limited. However, a recent case report addressed the use of [^{11}C]-BF-227 for visualization of myocardial amyloid deposits in a patient with ATTR amyloidosis (13).

CONCLUSIONS

Nuclear medicine imaging modalities are not only useful to provide an entire overview of extent and distribution of amyloid deposits. They may also be helpful in identifying consequences of amyloid deposition on the sympathetic innervation of the myocardium.

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