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Technetium pyrophosphate myocardial uptake and peripheral neuropathy in a rare variant of familial transthyretin (TTR) amyloidosis (Ser23Asn): a case report and literature review

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Abstract

We report the fourth case of transthyretin amyloidosis (ATTR) Ser23Asn in a 41-year-old Ecuadorian male. He has a pedigree that spans 7 generations and involves 24 family members who suffered early cardiac death. Salient presenting symptoms were fatigue, shortness of breath, and peripheral neuropathy. The diagnosis of cardiac amyloid was confirmed by immunohistochemical staining of an endomyocardial biopsy, genotyping, and by technetium pyrophosphate (^{99m}Tc-PYP) scintigraphy, which remains to be established as a reliable tool to visualize myocardial amyloid involvement in patients with the Ser23Asn TTR variant. The patient underwent successful combined heart and liver transplant. We add to the current ATTR literature that in patients with the rare Ser23Asn mutation, peripheral nerve in addition to cardiac involvement can occur and ^{99m}Tc-PYP scintigraphy can be used as an imaging modality to visualize myocardial amyloid.

Keywords

transthyretin amyloid; ATTR; Ser23Asn; technetium pyrophosphate; peripheral neuropathy

Background

ATTR, a rare but usually fatal disorder, is the most frequent cause of autosomal-dominant hereditary systemic amyloidosis.[1, 2] Mutations in TTR, a tetrameric plasma transport protein for thyroid hormone and retinol-binding hormone/vitamin A, [3] cause misfolded TTR variants that aggregate to form abnormal insoluble fibrils. Deposition of these fibrils in organs and tissues is associated with clinical syndromes including nephropathy, polyneuropathy, ophthalmopathy, and cardiomyopathy, with varying phenotypic expression

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related to over 100 delineated mutations.[4–7] Among the rarest TTR variants is Ser23Asn, which to the best of our knowledge, has only been reported three times in the literature (Table 1).[8–10]

Case Report

In 2010, a 41 year old Ecuadorian man of Spanish and Italian extraction was referred to the Advanced Cardiac Care Center at Columbia University after endomyocardial biopsy genotyping revealed amyloidosis secondary to the familial transthyretin mutation Ser23Asn. His presenting symptoms were fatigue and shortness of breath, which had worsened over the past year. In addition, he had bilateral foot numbness and burning pain without weakness or gait ataxia. Family history revealed that within 7 generations, 29 individuals succumbed to cardiac related disease (Figure 1). Of these, 24 died before age 55. The mode of inheritance is autosomal dominant.

On physical exam, blood pressure was 90/60 without postural change. He had JVP to 8 cm, a regular cardiac rhythm with a II/VI systolic murmur at the left sternal border with an S4 gallop. His lungs were clear and he had no peripheral edema. There was no macroglossia or palpable hepatosplenomegaly. Neurologic exam showed normal strength and vibration sense but bilateral loss of pinprick sensation in the distal feet and absent ankle reflexes. Laboratory studies were notable for a brain natriuretic peptide (BNP) of 391 pg/ml and a troponin of 0.04 ng/mL, but revealed no other cause of neuropathy, including testing for diabetes, impaired glucose tolerance, celiac disease, rheumatoid arthritis and syphilis. ESR, quantitative immunoglobulins, and ANA were normal.

ECG showed a normal sinus rhythm, a PR interval of 176 msec, QRS 136 msec, QTc 512 msec, a right bundle branch block, left atrial enlargement, and Q waves in I, avL, V1, and V2. Transthoracic echocardiogram (TTE) 1 year prior had shown an ejection fraction (EF) of 60–65%, mild left atrial enlargement at 4.8 cm, moderately increased left ventricular (LV) wall thickness, and a small effusion. Four months after this TTE, cardiac MRI had shown severe LVH, an EF of 38%, EDV 181 mL, ESV 111 mL, LV mass of 329 g with severely increased septal (IVS) and posterior (LVPW) wall thickness of 19 mm, hyperenhancement, and a large pericardial effusion. T2* was greater than 40 msec, not suggestive of significant iron overload. Within 16 months, TTE had shown a drop in EF to 25%, and IVS and LVPW of 21 mm, BNP correspondingly rose to 502 pg/ml and peaked at 699 pg/ml. The marked progression of cardiac involvement over a short time course prompted a cardiac catheterization, which showed normal coronaries with an EF of 30%. Immunohistochemical staining of an endomyocardial biopsy was positive for TTR amyloid (Figure 2) and TTR gene sequencing revealed a serine to asparagine mutation at position 23 that is associated with TTR cardiomyopathy.(8)

He underwent ^{99m}Tc-PYP scintigraphy as part of a clinical trial investigating the utility of this nuclear imaging modality in the differential diagnosis of cardiac amyloid. Planar imaging with ^{99m}Tc-PYP was performed with a dual head Phillips Precedence camera equipped with low energy, high resolution collimators. He received 20–30 mCi of ^{99m}Tc-PYP intravenously and two supine views were obtained one hour later: anterior/lateral and

left anterior oblique (LAO). About 2,000,000 counts were collected over 5 minutes from anterior/lateral and LAO views. The tracer distribution pattern was first evaluated in terms of diffuse versus focal localization. Semi-quantitative analysis of heart retention was calculated by drawing region of interest (ROI) over the heart. All ROI's were corrected for background counts. Myocardial retention was visually scored according to the following rubric: 0 = absent, 1 = mild, 2 = moderate, 3 = strong. Image analysis was independently performed by an experienced nuclear cardiologist blinded to all patient data. The study revealed predominant diffuse tracer retention with a visual score of 3 in the myocardium (Figure 3).

To evaluate his peripheral neuropathy, nerve conductions were normal and electromyography (EMG) showed only signs of chronic denervation in the tibialis anterior. Medical management included hydrochlorothiazide, spironolactone, and diflunisal, a nonsteroidal anti-inflammatory shown to stabilize the transthyretin tetramer.[11] Due to the severity of his infiltrative cardiomyopathy secondary to the transthyretin mutation, the malignant natural history of his Ser23Asn genotype, impressive family history with 24 cases of premature cardiac death, and worsening neuropathic symptoms, he underwent successful heart and liver transplant in May 2011. This was complicated by hepatic artery thrombosis 1 month post-operation, a previously reported complication of liver transplantation in this cohort, [12] requiring TPA and hepatic artery stents. Liver function tests normalized and he recovered well.

Two months after his liver transplant, BNP was 304 pg/ml, decreased from a pre-transplant peak of 699 pg/ml. Bimonthly endomyocardial biopsies for 5 months post-transplant showed no evidence of acute rejection. However, the pain and numbness in his feet continued. A skin biopsy revealed decreased epidermal nerve fiber density compatible with a small fiber neuropathy. Fiber counts in the calf were reduced to 3.7 epidermal nerve fibers (enf)/mm where the 5th percentile of normal is 5. Fiber counts were normal at the proximal thigh at 11.5 enf/mm with the 5th percentile being 8. There were short length, small caliber, complex branching, focal swelling and uneven distribution of axons. Congo red staining for amyloid was negative.

Discussion

In this fourth case of the rare hereditary TTR amyloid variant, Ser23Asn, we highlightan extensive family pedigree, the patient's peripheral neuropathy, our employment of ^{99m}Tc-PYP scintigraphy as a diagnostic modality, and successful combined heart and lung transplant.

Pedigree analysis revealed 24 individuals who suffered early cardiac death in a family spanning 7 generations with two consanguineous unions. Genotypic evidence is limited only to the proband and two other family members and we acknowledge that other cardiac risk factors or disease may have also contributed to cardiac deaths. However, the disproportionate degree of early cardiac pathology in this pedigree relative to that of the general population suggests that many of the deaths may also be attributed to ATTR. Symptoms at presentation in all four Ser23Asn patients described to date were consistently associated with heart failure – fatigue, shortness of breath, and chest discomfort with non-

invasive imaging suggesting cardiac involvement – but our patient also presented with peripheral neuropathy (Table 1). While some TTR mutations cause specific clinical syndromes, there is considerable variation in disease presentation. Sensorimotor polyneuropathy is a major feature of several types of systemic amyloidoses, hence the name, familial amyloidotic polyneuropathy (FAP). It is most consistently observed in patients with ATTR where the degree of neurologic versus cardiac involvement seems to be genotype dependent. In the most common V122I mutation, significant neuropathy is rare and cardiomyopathy tends to occur late, whereas in the V30M mutation, neuropathy tends to occur early and cardiomyopathy occurs late. Classically, as in this case, the neuropathy begins with small-fiber dysfunction in the lower extremities with early loss of temperature sensation and dysesthesias. Motor function is preserved until sensory neuropathy becomes severe. The level of sensory loss slowly ascends from the feet to the knees at which point sensory symptoms also manifest in the upper extremities. Autonomic neuropathy can also occur relatively early and can cause sexual impotence in men, gastrointestinal dysmotility, and bladder retention. EMG, a valuable tool for detecting peripheral neuropathy, showed chronic denervation in the tibialis anterior but no median neuropathy at the wrist to suggest carpal tunnel syndrome. He was transplanted before autonomic, motor, or upper extremity neuropathy could ensue.[13]

Peripheral neuropathy may not necessarily recover after orthotopic liver transplant (OLT) though, and may in fact worsen. Wild-type TTR produced by the transplanted liver can continue to deposit as cardiac amyloid after OLT.[7] In patients who undergo combined heart and liver transplant, it is thought that amyloid does not deposit in the heart graft, presumably due to lack of preformed amyloid nidus that facilitates addition of wild-type deposits. However, amyloid involvement can occur in other organ systems including peripheral nerves where some degree of amyloid has already deposited by the time of transplant. And while outcomes in Ser23Asn patients have yet to be elucidated, progression of amyloidosis post-OLT should be considered in light of the aggressive nature of this particular TTR variant; all four cases reported presented with clinically debilitating symptoms in their early 40s.

OLT has also been reported to arrest progression and allow for neurologic recovery in patients with FAP.[15] This observation supports both the axonopathic (mechanical) and metabolic (toxic) mechanisms of FAP.[16, 17] In the former, amyloid deposits accumulate and infiltrate epineural and endoneural connective tissues and the vasa nervosum.[18, 19] Teased fiber studies have shown a predominance of axonal degeneration in which amyloid deposits indented nerve fibers, suggesting local compression as a pathophysiologic process of neuropathy.[20] In addition, endoneural hypoxia resulting from infiltration of endoneural microvasculature has been suggested as a neuropathic process.[21] All of these mechanical processes are plausible in the classic distal-to-proximal pattern of neuropathy as longer axons would be subject to more damage than shorter axons. The fact that our patient's neuropathy has not yet improved post-OLT supports this theory as the process of biochemical turnover of amyloid deposits is extremely slow.[22] Toxic-metabolic processes may also play a role in neuropathy. The degree of amyloid fibril formation is thought to be much less than would be expected with the extent of neuronal damage and Wallerian-type degeneration. This suggests that another mechanism, namely amyloid toxicity to the dorsal

root ganglia with disruption of axonal transport mechanics, [23, 24] contributes to amyloid neuropathy. The classic distal-to-proximal pattern of neuropathy is also consistent with this theory as the longest neurons are most susceptible to damage.

The diagnosis of cardiac amyloid was confirmed by immunohistochemical staining of an endomyocardial biopsy that was strongly positive for amyloid. Less invasive biopsy sites than the heart such as abdominal fat or bone marrow are ideal for diagnosis, but the utility of these tests seems to be questionable in Ser23Asn patients (Table 1). In the two patients who received an abdominal fat biopsy, one had a positive test and the other was a false negative. In the latter, bone marrow biopsy was also negative. Unfortunately, for a significant percentage of patients with ATTR cardiac amyloidosis, fat pad biopsies have a low yield. The performance of more sensitive endomyocardial biopsy has been restricted to large centers with significant expertise not just in performing the procedure, but also in the pathologic evaluation of the amyloid type, which is critical to achieving an accurate diagnosis and implementing the appropriate treatment. Therefore, more sensitive noninvasive diagnostic tests are needed.

Several nuclear imaging modalities have been employed to visualize myocardial involvement. Most clinical evidence has been established for the use of ^{123}I -metaiodobenzyl guanidine (^{123}I -MIBG), $^{99\text{m}}\text{Tc}$ -aprotinin, and $^{99\text{m}}\text{Tc}$ -labelled phosphate derivatives, especially in the differential diagnosis and etiology of cardiac amyloidosis.[25] Since its introduction in 1974, non-invasive $^{99\text{m}}\text{Tc}$ -PYP scanning has been shown to be a highly sensitive indicator of myocardial necrosis in acute myocardial infarction and demonstrates dense biventricular tracer uptake in patients with cardiac amyloidosis.[26–28] The utility of these scintigrams is greater in ATTR cardiac amyloid than in AL disease. Myocardial uptake is global compared with other infiltrative diseases such as hemochromatosis or sarcoidosis in which uptake is focal.

We report for the first time that $^{99\text{m}}\text{Tc}$ -PYP scintigraphy showed strong myocardial tracer uptake in patients with the rare ATTR Ser23Asn mutation, suggesting that this imaging modality can successfully visualize myocardial ATTR amyloid in Ser23Asn patients. In most cases, positive myocardial scans seem to depend on a critical mass of amyloid, which is demonstrated by the direct relationship between LV wall thicknesses and scan positivity. However, the precise mechanism of pyrophosphate uptake in ATTR amyloidosis remains unclear. It has been suggested to be related to increased calcium concentration in amyloid-infiltrated tissue, as $^{99\text{m}}\text{Tc}$ -PYP studies have demonstrated a strong correlation between calcium accumulation and radiotracer uptake in tissues.[29] There are no systematic studies that specifically compare the utility of $^{99\text{m}}\text{Tc}$ -PYP in ATTR versus AL cardiac amyloid. Our own preliminary data suggest that $^{99\text{m}}\text{Tc}$ -PYP has a high affinity for ATTR cardiac amyloid from both V122I mutation and wild type disease and it has no affinity for AL cardiac amyloid and thus could be useful for identifying subjects with ATTR cardiac amyloid.

This case offers several insights into the diagnosis, inheritance, and symptomatology of the rare TTR Ser23Asn variant. First, our pedigree analysis suggests that Ser23Asn TTR variant is aggressive, particularly in offspring of consanguineous unions. Second, we report that in addition to myocardial involvement, Ser23Asn amyloid also deposits in peripheral nerves,

elucidating that this mutation can have heart failure *and* neuropathic symptomatology. Third, ^{99m}Tc -PYP scintigraphy revealed for the first time that Ser23Asn mutants display dense myocardial tracer uptake, suggesting that this noninvasive nuclear imaging modality may be employed in the diagnosis of ATTR in Ser23Asn mutants.

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Abbreviations

ATTR	transthyretin amyloidosis
BNP	brain natriuretic peptide
EF	ejection fraction
EMG	electromyography
ENF	epidermal nerve fibers
FAP	familial amyloidotic polyneuropathy
^{123}I-MIBG	^{123}I -metaiodobenzyl guanidine
LV	left ventricle
LAO	left anterior oblique
OLT	orthotopic liver transplant
ROI	region of interest
^{99m}Tc-PYP	technetium pyrophosphate scintigraphy
TTE	transthoracic echocardiogram

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Figure 1.

Inheritance of cardiac disease across 7 generations in an Ecuadorian patient of Spanish and Italian descent. 29 individuals succumbed to cardiac-related disease. Of these, 24 died before the age of 55 (current age or age at death, 'd', is specified underneath each individual). ATTR Ser23Asn was confirmed in the proband (arrow), who underwent a heart/liver transplant in 2011. The mode of inheritance appears to be autosomal dominant with anticipation. Consanguineous unions are seen in generations 2 and 3.

Figure 2. Immunohistochemical staining of an endomyocardial biopsy is strongly positive for TTR (A) as compared with AA amyloid (B), kappa amyloid (C), and lambda amyloid (D).

Figure 3.
 ^{99m}Tc -PYP planar myocardial imaging (anterior view) revealed dense myocardial tracer uptake in this ATTR Ser23Asn mutant (C) as compared with a patient with no history of cardiac amyloid or heart failure (A), and a patient with heart failure without cardiac amyloid (B).

Table 1

Profiles of ATTR Ser23Asn case reports to-date.

CASE	GROUP	ORIGIN	AGE (YRS)	SYMPTOMS AT PRESENTATION	FAMILY HISTORY	DIAGNOSIS	ORGANS AFFECTED
1	Connors et al.	Portugal	44	F	No	AFBx (+) EMBx (+)	Heart
2	Daoko et al.	Peru	41	CP, SOB	SCD	AFBx(-) BMBx (-) MRI (+) EMBx (+)	Heart
3	Mueller et al.	Italy/Germany	46	CP, SOB	German: No; Italian: Incomplete	^{99m} Tc-DPD(+) EMBx(+)	Heart
4	Castaño et al.	Ecuador (Italy/Spain)	41	F, SOB, PN	PCD	^{99m} Tc-PYP(+) EMBx(+)	Heart, PN

F = fatigue, CP = chest pain; SOB = shortness of breath; PN = peripheral neuropathy; SCD = sudden cardiac death; PCD = premature cardiac death; AFBx = abdominal fat biopsy; BMBx = bone marrow biopsy; EMBx = endomyocardial biopsy; ^{99m}Tc-DPD= technetium-3,3-diphosphono-1,2-propanodicarboxylic acid scintigraphy; ^{99m}Tc-PYP = technetium-pyrophosphate scintigraphy