Cardiac Sympathetic Denervation in Transthyretin-Related Familial Amyloidotic Polyneuropathy: Detection with Iodine-123-MIBG

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In familial amyloidotic polyneuropathy (FAP), the peripheral nervous system is predominantly impaired. Cardiac sympathetic function has not been directly assessed. A 65-yr-old man with severe peripheral neuropathy due to primary systemic amyloidosis was studied. Echocardiograms and scintigraphic examinations with ^{201}Tl and ^{99m}Tc-pyrophosphate demonstrated highly thickened but normally perfused left ventricular walls with intense diffuse amyloid deposits. No definite myocardial activity of [^{123}I]metaiodobenzylguanidine (MIBG) was detected in any cardiac region, indicating lack of sympathetic nerve endings. Despite maintained cardiac contractility, left ventricular diastolic performance and heart rate variability assessed by power spectral analysis were markedly depressed. Thus, the myocardial defect of MIBG activity may provide direct evidence of impaired cardiac sympathetic nerve endings due to amyloid deposits in FAP.

Key Words: iodine-123-metaiodobenzylguanidine; familial amyloidotic polyneuropathy; cardiac amyloidosis; cardiac sympathetic nerve function

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Familial amyloidotic polyneuropathy (FAP) is a rare systemic disorder in which the peripheral nervous system becomes markedly impaired, particularly in the extremities, due to amyloid deposition. Recent studies have revealed that a genetic variant of normal prealbumin, namely transthyretin (TTR), causes autosomal dominant hereditary systemic amyloidosis and is related to several clinical features of this disease, including peripheral neuropathy, cardiac amyloidosis, amyloid kidney and ocular alterations (*1–4*). Cardiac amyloidosis causes conduction disturbances, arrhythmias, restrictive cardiomyopathy and low output heart failure. In a FAP patient, peripheral ascending neurons were predominantly involved; cardiac manifestations were less severe and cardiac sympathetic dysfunction has not been definitely determined. Iodine-123-metaiodobenzylguanidine ([^{123}I]MIBG) can accumulate specifically in postganglionic sympathetic neurons in the same manner as norepinephrine and, consequently, the myocardial activity and kinetics of [^{123}]I MIBG possibly reflect normal structure and function of the cardiac sympathetic nerves (*5*). Rapid clearance of myocardial [I-123] MIBG has been observed in patients with autonomic neuropathies, such as Shy-Drager syndrome, idiopathic orthostatic hypotension and diabetes mellitus (*6–8*). Markedly reduced MIBG uptake has likewise been reported in transplanted human hearts (*9*).

We studied a FAP patient with a methionine substitution for valine at position 30 of the transthyretin sequence (TTR Met 30). The combined use of three myocardial imaging protocols—^{201}Tl, ^{99m}Tc-pyrophosphate and [I-123] MIBG—demonstrated the unique characteristics of his myocardial tissues, i.e., the left ventricle was normally perfused and contracting, but it was markedly thickened and totally denervated.

CASE REPORT

A 65-yr-old man was admitted with numbness and disability in his extremities. He had no past history of cerebrovascular or cardiac accident, drug abuse, alcoholism, or endocrinologic, metabolic, inflammatory or other systemic disorders. On admission, he had normal sinus rhythm with a rate of 76/min and a blood pressure of 160/80 mmHg in the supine position and 140/78 mmHg in the upright position. Neurological examination disclosed markedly reduced light and tendon reflexes and highly impaired sensory and motor systems in his extremities; by contrast, there was no evidence of an impaired central nervous system except for the light-reflex abnormality. No other physical abnormalities were detected. Conductance velocities of peripheral sensory nerves were not measurable in the lower extremities; velocities were markedly reduced in the upper limbs, and the amplitudes were quite low. There were no abnormalities in hematology, renal function and serologic, metabolic and hormonal tests. Urinalysis showed neither proteinuria nor Bence-Jones protein, and a bone marrow test showed no evidence of plasma cell dyscrasia. Histology of gastric biopsy specimens stained by hematoxylineosin and Congo red clearly demonstrated deposition of amyloid protein in the muscularis mucosae and small vessel walls. Myocardial biopsy was not performed because of disability due to severely symptomatic peripheral neuropathy. TTR Met 30 was detected in

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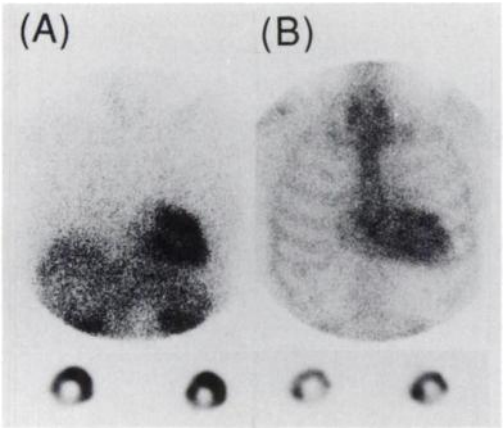

FIGURE 1. Anterior planar scan (upper panels) and short-axial tomograms (lower panels) with ^{201}Tl (A) and ^{99m}Tc-pyrophosphate (B). The left ventricular walls are symmetrically thickened but normally perfused, and intense and diffuse positivity of pyrophosphate is observed over the heart, particularly in the left ventricle, as much as in adjacent bone.

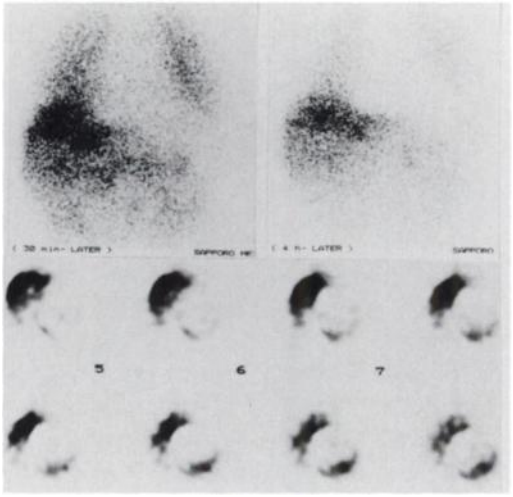

FIGURE 2. Iodine-123-MIBG scans of the anterior chest and abdomen 30 min (upper left panel) and 4 hr (upper right panel) postinjection show no definite myocardial uptake in any cardiac region despite the activities normally observed in the liver and lungs. Note that the serial transverse tomograms on the early scan (lower panels) clearly support the lack of positive myocardial MIBG.

plasma, however, by radioimmunoassay using monoclonal antibodies established by Araki et al. (*10–11*). Family investigation showed no possibility of peripheral neuropathy or cardiac amyloidosis. From these findings, the diagnosis of a sporadic case of TTR-related familial amyloidotic polyneuropathy type 1 (lower limb type) (*3,4*) was established.

The electrocardiogram (ECG) revealed first degree atrioventricular block and bifascicular block. Abnormal Q waves were found in leads II, III, and aVF, and the T wave was inverted in leads V4-6. A chest radiograph showed a cardiothoracic ratio of 54% and no pulmonary venous congestion. Holter monitoring revealed no serious ventricular complexes. Two-dimensional echocardiograms revealed symmetrically increased wall thickness of the left ventricle with a characteristic granular sparkling appearance but a normally maintained left ventricular (LV) cavity size as well as normal systolic function. LV fractional shortening was 40%, and the end-diastolic thicknesses of the LV posterior wall and the interventricular septum were 18 mm and 16 mm, respectively. Although neither asynergic wall motion nor valvular disease were detected, Doppler ultrasound showed highly reduced early velocity (E) and increased late velocity (A) of transmitral flow. A/E increased to 1.6.

Radionuclide ventriculography showed a normal LVEF (70%), no asynergy, but highly reduced LV diastolic function; peak filling rate was 2.08 (EDC/sec) and the ratio of peak filling rate to peak ejection rate was 0.62 (*12*). Myocardial thallium scintigraphy demonstrated markedly thickened LV walls but no definite hypoperfused area (Fig. 1A). PYP scanning with 555 MBq of ^{99m}Tc revealed intense diffuse uptakes in both ventricular walls (Fig. 1B). Iodine-123-MIBG (111 MBq) was injected intravenously during resting and fasting conditions. Planar and tomographic scans were obtained 30 min and 4 hr after injection. No definite myocardial uptake was detected. In contrast, the activities in the liver and lungs were normal (Fig. 2). In addition, power spectral analysis of heart rate variability showed no detectable high-frequency spectral component, but a markedly reduced low-frequency component, suggesting highly damaged vagal and sympathetic activities of the heart. These findings indicate that neurological abnormalities were present not only in the peripheral nervous system but also in the cardiac autonomic nervous systems. Although systolic performance was reduced during this 3-yr follow-up period, in which LVEF fell from 70% to 55% and fractional shortening fell from 40% to 32%, the patient survives with advanced peripheral neuropathy but no cardiac symptoms.

DISCUSSION

In addition to intense and diffuse positivity of ^{99m}Tc-PYP scanning, markedly impaired sympathetic innervation was clearly demonstrated by ^{123}I MIBG scanning with TTR Met 30.

Despite its limited diagnostic value, a positive ^{99m}Tc-PYP scan has been demonstrated in cardiac amyloidosis (*13–14*). Although myocardial tissue diagnosis of amyloidosis was not made in this patient, massive myocardial uptake of pyrophosphate, a characteristic granular sparkling appearance on echocardiograms, and amyloid deposits in the GI tract strongly support amyloid infiltration into the heart. Pyrophosphate interacts specifically with amyloid fibers because of their calcium affinity (*14*). Amyloid proteins accumulated extracellularly can be attributed to myocardial cell atrophy and to the loss of membrane integrity leading to necrosis and replacement of myocytes. LV systolic performance and myocardial perfusion in this case, however, indicate that viable myocytes are functioning sufficiently, although massive amyloid deposits restrict LV diastolic filling and disturb conduction systems.

It is of great interest that neither early nor late scans demonstrated definite MIBG uptake in any cardiac region. Several mechanisms might account for the markedly and globally reduced MIBG uptake. Myocardial ischemia or coronary artery disease is unlikely because there is no evidence of chest pain, asynergic wall motion, or reduced thallium perfusion. Accelerated clearance of MIBG from the heart as seen in autonomic neuropathy (*5,7*) and dilated cardiomyopathy (*15*) appears even less possible. Scanning

during the first 30 min postinjection mainly reflects the greater influx of MIBG into extraneuronal spaces in myocardial tissue rather than into the neuronal component. Therefore, myocardial MIBG uptake was assessed 30 min and 4 hr postinjection in our patient. The latter scan displays neural uptake of MIBG more specifically. The lack of MIBG positivity, even in the early image, suggests loss or destruction of cardiac sympathetic nerve endings rather than functional abnormalities such as an increase in release, metabolism, turnover of norepinephrine (MIBG) or alterations in the storage mechanism (*16*). The findings of pyrophosphate deposits and lack of MIBG positivity may indicate amyloid infiltration into cardiac sympathetic nerve endings, such as that occurring in peripheral neurons of the extremities. In view of the findings of Sisson et al. (*7*) and our experience (unpublished observation) with the Shy-Drager syndrome, the possibility that total cardiac denervation derives from injury to preganglionic fibers of the sympathetic nervous system cannot be ruled out completely. The markedly depressed cardiac autonomic function revealed by the depressed low- and high-frequency components of heart rate variability suggests cardiac sympathetic denervation. These characteristics appear quite similar to those of transplanted hearts (*9*).

Several implications follow from the lack of MIBG positivity in a FAP patient. First, the finding indicates cardiac sympathetic nerve involvement in TTR Met 30-related FAP. Like peripheral nerves, cardiac sympathetic nerve endings may also be susceptible to amyloid protein-related nerve damage. Second, amyloid deposits and sympathetic nerve dysfunction may possibly exacerbate arrhythmias and conduction disturbances leading to sudden cardiac death. Third, impaired cardiac sympathetic regulation may further impair diastolic performance due to massive amyloid deposition or it may blunt the compensatory mechanism for exercise intolerance and heart failure. Fourth, cardiac sympathetic nerve involvement may define the degree of progression of the disease and determine the prognosis in a FAP patient. The clinical features of LV diastolic dysfunction but normally maintained thallium perfusion and systolic function in this case may be an early consequence of myocardial amyloid deposition prior to a deteriorative clinical outcome. Further experience is necessary, however, to establish the clinical implications of impaired cardiac sympathetic nerves related to TTR Met 30 FAP.

Markedly reduced MIBG uptake on early and delayed images appears to be associated with functional and anatomical abnormalities of cardiac sympathetic neurons due to amyloid deposits in TTR-related FAP type 1. MIBG scintigraphy may be an effective tool for direct and visual assessment of cardiac sympathetic innervation and to exploring the mechanisms of impairment by the combined use of other noninvasive methods.

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