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Peer reviewed

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Running Title: Amyloid Polyneuropathy

Abstract

Introduction: Amyloidosis derived from transthyretin (TTR) molecules is typically caused by mutations of the *TTR* gene.

Case or Methods: We describe an elderly patient with a severe length-dependent polyneuropathy that unexpectedly proved to be caused by wild-type transthyretin amyloidosis.

Results: The diagnosis was made by muscle biopsy, since no amyloid deposits were found in the biopsied nerve segment. Most cases of wild-type transthyretin amyloidosis occur in elderly patients with cardiomyopathy, but a few cases of polyneuropathy have been reported.

Discussion: This entity is especially noteworthy in light of emerging treatment options for hereditary transthyretin amyloidosis, which are likely also to be beneficial in wild-type disease.

Senile systemic amyloidosis (SSA), or wild-type transthyretin (*TTR*) amyloidosis, is associated most commonly with cardiomyopathy and carpal tunnel syndrome. Polyneuropathy has not been thought to occur in this form of amyloidosis. However, the Transthyretin Amyloidosis Outcomes Survey (THAOS), an international multicenter longitudinal study, recently reported sensory neuropathies in one-third of patients with SSA[1]; a few other cases of SSA with polyneuropathy have been reported. [2,3,4]   Here, we describe the case of a patient with SSA who exhibited a severe, painful sensorimotor polyneuropathy.

CASE REPORT

An 84-year-old woman with a history of coronary artery disease, congestive heart failure, atrial fibrillation, and borderline diabetes was admitted to the hospital complaining of progressive difficulty walking for 4 years. For several years she had deep burning pain and numbness in her legs to the level of the mid-shins. She used a cane initially and required a walker 2 years later. She was on no medications associated with a toxic neuropathy. Neurological examination 14 months prior to current presentation demonstrated full strength except for moderate weakness of dorsiflexion and eversion of the left foot. There was impaired sensation to light touch and pinprick from the mid-shins distally. Vibratory perception was decreased in the toes. Computed tomography of the lumbar spine showed hypertrophic changes with marked stenosis, and she was given a diagnosis of spinal stenosis; no treatment was given. Her leg numbness and weakness continued to worsen; for 6 weeks she had difficulty arising from a chair or her bed, and for 1 month she was unable to walk. The upper extremities were not involved. Her mother (deceased) was said to have developed a polyneuropathy in her 80s, while her sister had an unspecified neuropathy; neither condition was disabling.

Neurological examination revealed severe weakness and atrophy of the distal lower extremities with no movements in the feet, and mild weakness of the hips and thighs. The upper extremities and neck muscles were normal. Reflexes were absent in the lower extremities. Proprioception was absent in the toes, and vibratory perception was absent in the feet up to the ankles. Other sensory modalities were not tested. She was unable to sit or stand without assistance.

Laboratory studies in the hospital revealed a HgbA1c of 6.5%. Serial blood glucose monitoring (fasting glucose and HgbA1c) showed glucose intolerance for several years prior, with the highest HgbA1c (6.7%) about 4 months prior to presentation. She had normal serum creatine kinase, TSH, vitamin B12, ANA, and ANCA. Serum protein immunoelectrophoresis showed biclonal IgG kappa paraproteins, and electrocardiogram showed atrial fibrillation. Echocardiogram demonstrated a severely dilated left atrium and mild concentric left ventricular hypertrophy. There was normal left ventricular size and ejection fraction (> 60%).

Nerve conduction studies of the lower extremities showed absent sural sensory nerve action potentials, very low amplitude right fibular and bilateral tibial compound muscle action potentials (CMAPs) and absent left fibular CMAP. Electromyography showed acute denervation and chronic reinnervation below the knees and chronic reinnervation in the proximal lower extremities.

A right gastrocnemious muscle biopsy showed abundant deposits of congophilic amorphous material in the walls of perimysial and epimysial vessels, in the interstitium, and within hypertrophied muscle fibers (Fig. 1, A-D); this amyloid material stained with anti-TTR antibody

(Fig. 1, E-F), but was negative for κ and λ light immunochains and β-amyloid. Electron microscopy showed large deposits of 10.7 nm amyloid fibrils (Fig. 1, G-H) located both inside and outside of muscle fibers. In addition, there were marked neurogenic changes (fiber type grouping, grouped atrophy, subsarcolemmal nuclear aggregates, and frequent fibers with diffuse esterase staining). The right sural nerve biopsy showed moderately severe axonal neuropathy with a demyelinating component (50-80% loss of myelinated axons, a large population of thinly myelinated axons, and shortening of the intermodal distances on teased nerve preparation); however, no neural amyloid deposits were identified either on Congo red stain or by TTR immunohistochemistry.

With a diagnosis of TTR amyloidosis demonstrated by muscle biopsy, complete DNA sequence analysis of the *TTR* gene (including all coding regions and intron/exon boundaries; >99% sensitivity [5]) was performed at the Mayo Clinic Laboratory. No mutations were detected, indicating that the amyloidosis in this case was caused by wild-type TTR. The patient died of cardiac complications about a year following the diagnosis; no autopsy was performed.

DISCUSSION

Although the patient had a family history of polyneuropathy, genetic testing revealed that she had a nonfamilial form of amyloidosis. Furthermore, despite having a gammopathy on serum testing, light chain staining on immunohistochemistry was negative, ruling out primary systemic amyloidosis. Muscle biopsy established a diagnosis of TTR amyloidosis; DNA testing of the *TTR* gene was normal, indicating that the patient had wild-type TTR amyloidosis (SSA).

Mutations of the *TTR* gene cause most cases of hereditary amyloid polyneuropathy. The neuropathy is axonal and length-dependent, worse in the distal lower extremities. Small-diameter sensory fibers tend to be affected first, and neuropathic pain is often prominent, but eventually all sensory and motor fibers as well as the peripheral autonomic nervous system are affected. The age of onset tends to be in the third decade in Portugal and Japan but in the sixth or seventh decade in Sweden.[6] Sporadic cases also tend to have a later onset, even though most sporadic cases, when investigated, prove to have a *TTR* mutation.[7] Interestingly, the amyloid fibrils in hereditary TTR amyloidosis contain both mutant and wild-type TTR, and the percentage of wild-type TTR is higher (50%) in late-onset cases than in early-onset cases (30%).[8] This suggests that wild-type TTR may have a causative role in hereditary TTR amyloidosis.

Indeed, wild-type TTR can cause sporadic amyloidosis with no contribution from *TTR* mutations. This syndrome, known as senile systemic amyloidosis (SSA), is seen primarily in elderly men, although it can begin at a younger age; it is estimated to occur in up to 25% of individuals older than 80. Cardiac disease predominates in SSA, namely atrial fibrillation, cardiac conduction abnormalities, and hypertrophic cardiomyopathy.[9] Carpal tunnel syndrome is observed commonly and can precede cardiac manifestations.[10] TTR amyloid deposition has been shown in various other ligaments and tendons, as well as spinal cord and other organ systems.[11, 12, 13] In skeletal muscle, intramuscular amyloid deposition is usually present in the interstitium and blood vessel walls, but in this case it was also seen within muscle fibers; this has been reported in a few other cases.[14] Interestingly, the patient did not show evidence of myopathy on either clinical exam or electrodiagnostic studies despite abundant amyloid

deposition in muscle; it is possible that myopathic findings were obscured by concurrent severe neurogenic changes.

Most SSA reports are in the cardiology literature and make no mention of polyneuropathy. However, a few cases of SSA-associated polyneuropathy have been reported, and a recent summary of the Transthyretin Amyloidosis Outcomes Survey mentions (without providing details) sensory neuropathy in approximately 30% of 67 cases of wild-type amyloidosis, 15% with motor neuropathy and 25% with autonomic neuropathy. [1, 2, 3, 4] Our patient, therefore, does not appear to be unique, and in view of the surprisingly common occurrence of SSA in elderly men, more careful neurological surveillance of patients with cardiac SSA will be needed to obtain an accurate estimate of the incidence of wild-type TTR amyloid polyneuropathy.

This case highlights the limitations of nerve biopsy in diagnosing amyloidosis. Amyloid deposits were abundant in the muscle biopsy but absent in the nerve biopsy sample.   Indeed, due to the patchy nature of amyloid deposition in the nerve, a negative nerve biopsy does not negate the diagnosis of amyloid polyneuropathy; in fact, it is standard practice to make a diagnosis of amyloid polyneuropathy based on a compelling clinical presentation and proof of systemic amyloidosis based on involvement of other organ systems. In this case, the patient had the classic presentation of a painful, severe, and rapidly progressive polyneuropathy without a plausible alternative explanation and with evidence of system amyloid involvement, making amyloid polyneuropathy the most compatible diagnosis. Many other authors have emphasized that nerve biopsies may fail to show amyloid in a significant proportion of cases of amyloid polyneuropathy, and 2 recent series reported sensitivity of nerve biopsy to range from 63% to

83% (sample size 19 and 65 patients, respectively). [15, 16]   In a smaller study of 6 patients with amyloid polyneuropathy, no patients were found to have amyloid deposits in the sural nerve specimen, and amyloid was identified only after biopsy of another tissue type or another nerve.[17] In contrast, in another report muscle biopsy was positive in 10 out of 10 cases of polyneuropathy in primary systemic amyloidosis. [18] In clinically unclear cases, a combination of nerve and muscle biopsy may thus have a higher diagnostic yield than nerve biopsy alone. When systemic amyloidosis is suspected, fat pad biopsy may be the preferred initial diagnostic test, with a sensitivity of up to 80%, and relative ease and safety of the procedure. [19]

Although liver transplantation is ordinarily not a therapeutic option in SSA because of the advanced age of most patients, new treatments are being introduced. In particular, oral treatment with tafamadis and diflunisal, agents that stabilize the TTR tetramer and thus prevent the monomer from forming amyloid, was shown to be effective in stage III clinical trials. [20, 21] Tafamadis is currently approved for clinical use in European countries and Japan. While these drugs were studied in familial amyloidosis, their mechanism of action suggests that they should be effective in SSA as well.[22] Early diagnosis and treatment are important, because the drugs do not reverse amyoid deposition in tissues. Thus, it is important to keep in mind the possibility of SSA when evaluating elderly patients with a painful distal axonal polyneuropathy.

Abbreviations

transthyretin (TTR), senile systemic amyloidosis (SSA), Transthyretin Amyloidosis Outcomes

Survey (THAOS), compound muscle action potential (CMAP)

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Figure Legend

Fig. 1. Muscle biopsy findings. (A and B) Hematoxylin and eosin stain demonstrated widespread accumulation of amorphous pink material in blood vessel walls and large muscle fibers; the majority of muscle fibers had small angulated appearance. Arrows, vessel wall deposits; arrowheads, muscle fiber deposits. (C and D) The accumulated material was Congo red positive, indicative of its amyloid nature. Under regular light (C), amyloid deposits have salmon-pink color; apple green birefringence is evident under polarized light (D). (E and F) Amyloid deposits were TTR-immunopositive. (G and H) On electron microscopy, amyloid fibrils (average diameter, 10.7 nm) formed large deposits within and without muscle fibers; a large amyloid deposit in G is outlined with dashed lines and labeled with an asterisk. Scale bars, A-F, 50 μm; G, 2 μm; H, 0.5 μm.