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Letter to the Editor: New Observation

Severe Polyneuropathy in Hereditary Transthyretin Amyloidosis Caused by H90D Variant

Joshua Pierce[1], Karam Han[1], Harry V. Vinters[1,2], Jonathan E. Zuckerman[1] and Anasheh Halabi[2]

[1]Department of Pathology and Laboratory Medicine, David Geffen School of Medicine at University of California Los Angeles, Los Angeles, CA, USA and [2]Department of Neurology, David Geffen School of Medicine at University of California Los Angeles, Los Angeles, CA, USA

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Hereditary transthyretin amyloidosis (ATTRv) is a systemic disease caused by mutations in the *transthyretin* (*TTR*) gene.[1] Extracellular deposition of amyloid leads to sensorimotor polyneuropathy, autonomic dysfunction, gastrointestinal symptoms, and cardiomyopathy.[2] In the absence of disease-modifying therapies, severe manifestations of ATTRv can be fatal.[1] Over 130 pathogenic mutations have been identified in the *TTR* gene.[1] Genotype significantly influences clinical course and phenotype in ATTRv.[3] The missense *TTR* variant c.328C>G (ATTRv His90Asp, H90D, p.H110D) has been reported in one Irish kindred.[4] Other amino acid substitutions at this position have been designated as nonamyloidogenic.[5,6] For this reason, amino acid substitutions for histidine at this position are not classified as pathogenic. Here, we report an American family of Irish descent with autosomal dominant inheritance of ATTRv His90Asp. We provide definitive clinicopathologic evidence that this variant can cause ATTRv amyloidosis and should be classified as pathogenic.

A 74-year-old woman presented with early satiety, postural hypotension, episodes of intractable vomiting, fluctuating diarrhea, and constipation accompanied by 50-pound unintentional weight loss. She reported severe distal weakness and progressive sensory symptoms over 6 months. Her medical history was notable for ductal carcinoma *in situ* with lumpectomy, antiestrogen therapy, and local radiation therapy at 69 years of age. Family history revealed her father died at 70 years of age after approximately 5 years of significant gait impairment secondary to neuropathy. His autopsy reported amyloid as the cause of death; however, detailed autopsy report or site of amyloid deposition could not be acquired by his family. His death occurred three decades prior to the proband's presentation to us.

On physical examination, the proband was cachectic and hypotensive (92/58). Patient's weight was 55 kg relative to 72.6 kg documented 2 years prior. Neurologic examination demonstrated profound weakness in the distal lower extremities with symmetric absent vibration sense up to and including the tibial tuberosities, absent proprioception up to and including the ankles, and symmetric absence of pinprick and cold temperature throughout the legs and into the forearms. Electrodiagnostic studies demonstrated a severe, length-dependent, sensorimotor axonal polyneuropathy with superimposed bilateral median neuropathies at the wrist (i.e. carpal tunnel). The patient had reported numbness and tingling in the thumb and index finger of both hands approximately 1 year prior to presentation. From a cardiac standpoint, Tc-99m pyrophosphate scan was reported as strongly suggestive of ATTRv with H/CL ratio of 1.78. The patient required midodrine for symptomatic orthostatic hypotension. Holter monitor demonstrated premature atrial contractions. Fat pad biopsy was negative. Serum and urine immunofixation, protein electrophoresis, kappa, and lambda light chains were all unremarkable. Paraneoplastic antibody panel, Sjogren's antibodies, myeloperoxidasae antibody, and proteinase-3 were also negative. Commercially available targeted genetic sequence analysis with deletion and duplication testing reported two heterozygous variants of uncertain significance including *TTR*, c.328C>G (ATTRv His90Asp, p. His110Asp) and *INF2* c.3725_3728del (p. Thr1242Argfs*5). The patient died 9 months after presenting to us, approximately 4 and a half years from symptom onset.

The proband's postmortem examination (Figure 1) was remarkable for extensive deposition of amyloid demonstrated here as amorphous eosinophilic material within the myocardium (Figure 1a and 1c), as well as the arteries and arterioles of most organ systems with variable deposition in fibroadipose tissues (Figure 1e) throughout the body. Peripheral somatic and autonomic nerves demonstrated extensive endoneurial amyloid deposition illustrated in Figure 1b and Figure 1d demonstrating amyloid deposition in the sciatic and vagus nerves, respectively. Central nervous system examination demonstrated deposits predominantly in choroid plexus vessels (Figure 1f-h). Congo red stains were confirmatory of amyloid deposition (positive apple green birefringence under polarized light). Immunofluorescence studies for kappa and lambda light chain were performed and were negative. Immunohistochemical studies for prealbumin (transthyretin) were diffusely positive in amyloid deposits. Immunohistochemical studies for serum amyloid A demonstrated

Corresponding author: Anasheh Halabi, Department of Neurology, David Geffen School of Medicine at University of California Los Angeles, Los Angeles, CA, USA. Email: ahalabi@mednet.ucla.edu

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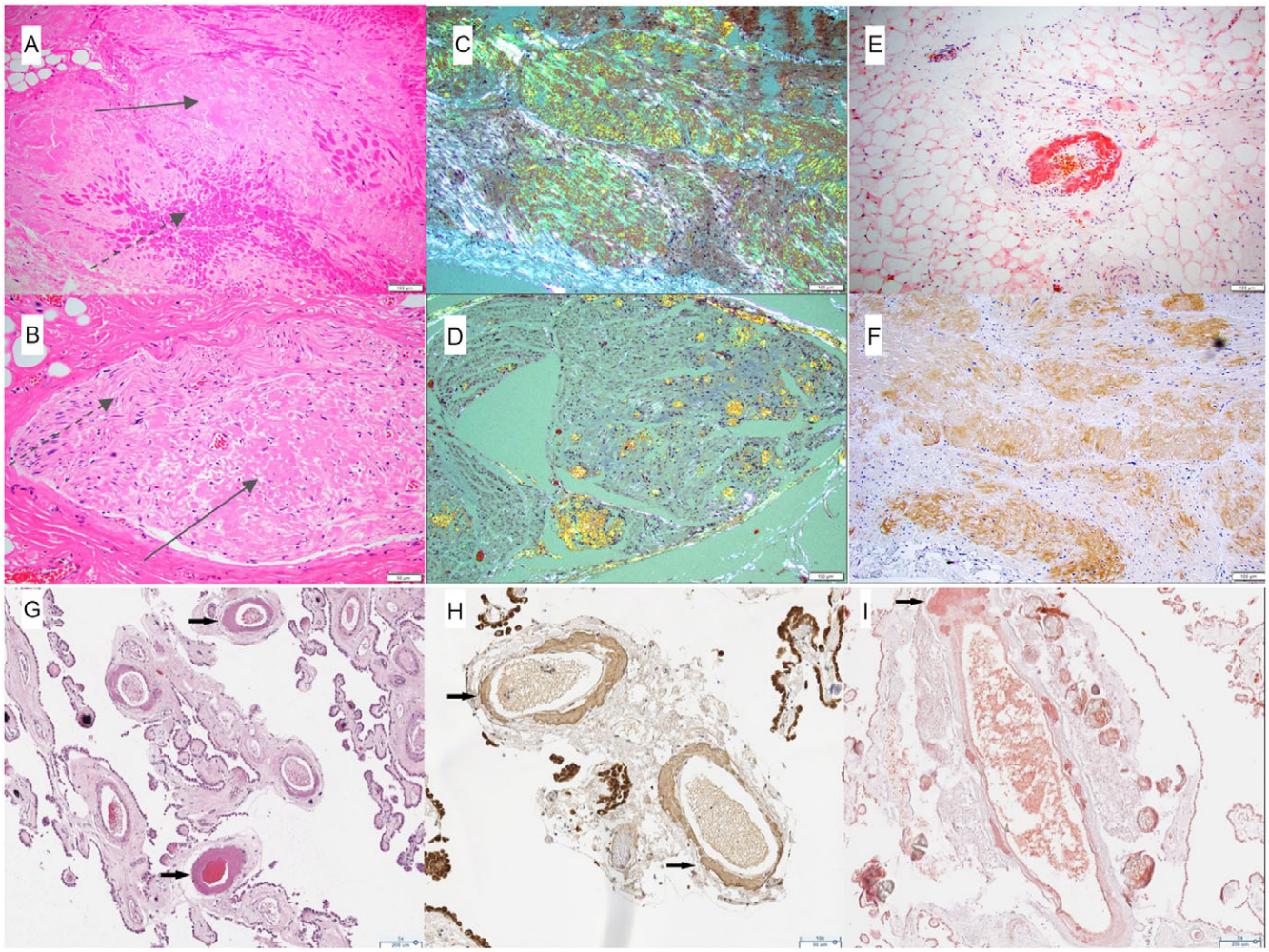

Figure 1: Postmortem examination. Extensive amyloid deposition seen here as amorphous eosinophilic material was present in multiple tissues. (a) Myocardium (hematoxylin & eosin, H&E stain; solid arrow amyloid; dashed arrow cardiomyocytes) (b) vagus nerve (H&E stain; solid arrow amyloid; dashed arrow nerve tissue), Congo red staining highlighted all amyloid deposits (c) myocardium, polarized light (d) sciatic nerve, polarized light (e) fibroadipose tissue and small artery, and (f) transthyretin immunohistochemical stain of cardiac tissue highlighting amyloid deposits (Brown colorimetric staining). (g) Choroid plexus vessels with prominent amyloid deposits in their walls. H&E-stained section shows cross-section of affected arteries. Arrows indicate amorphous eosinophilic material consistent with amyloid in vessel walls, confirmed by immunohistochemistry for transthyretin (h) and Congo red staining (i). The Congo red-stained deposits exhibited characteristic yellow-green birefringence on polarization.

nonspecific weak staining. Definite amyloid deposition within the parenchyma of liver, spleen, kidneys, adrenal glands, and luminal gastrointestinal organs was not present.

The proband's son presented at 53-years-old with numbness and paresthesia in the feet for approximately 1 year. His medical history was significant for carpal tunnel release on the left and the right at 44 and 45 years of age, respectively. Tissue blocks from these procedures were not available for Congo red staining. His electrodiagnostic studies demonstrated bilateral median neuropathies at the wrist (i.e. carpal tunnel) with no electrodiagnostic evidence of a sensorimotor axonal polyneuropathy. Tc-99m pyrophosphate scan was not suggestive of amyloidosis (H/CL ratio 1.27). Holter monitor demonstrated no evidence of ventricular arrhythmias but did show occasional episodes of supraventricular tachycardia lasting 5–14 beats and a 2.3% burden of supraventricular ectopy. Fat pad biopsy was negative. Bone marrow biopsy demonstrated vessels with amorphous eosinophilic deposits in their vascular wall that were Congo red positive and showed apple-green birefringence under polarized light. There were two foci of Congo red positive amorphous deposits within otherwise unremarkable marrow. Gallbladder pathology from cholecystectomy performed during hospitalization for cholecystitis was Congo red positive with 1–2 foci of amorphous eosinophilic material within small vessel walls showing green birefringence under polarized light microscopy consistent with focal amyloid deposition. Commercially available targeted genetic sequence analysis of *TTR* demonstrated the same ATTRHis90Asp variant as the proband.

The ATTRHis90Asp variant is not presently classified as pathogenic. This family demonstrates autosomal dominant inheritance across three generations with clinical features of ATTRv amyloidosis. The severity of clinical features is corroborated by the significance of amyloid deposition on postmortem examination. Both the proband and her father developed clinically significant symptoms in their late 60s and early 70s. For this reason, we suspect the proband's son is early in his course. The clinicopathologic evidence

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supporting the pathogenicity of ATTRHis90Asp is significant. Taken together with the Irish kindred reported by Jimenez-Zipeda et al.,[4] there is substantial evidence supporting the classification of ATTRHis90Asp as pathogenic, granting patients with this variant access to life-saving treatments.

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