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Case Review

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Demyelinating Neuropathy in a Patient Treated With Revusiran for Transthyretin (Thr60Ala) Amyloidosis

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Abstract

Transthyretin amyloidosis patients develop length-dependent peripheral neuropathy, autonomic dysfunction, and restrictive cardiomyopathy associated with deposition of amyloid fibrils in these tissues. Despite advances in management over the past decade, this disorder causes profound debilitation and ultimately proves fatal. In this report, we describe a man with late-onset cardiac amyloidosis due to a transthyretin Thr60Ala mutation who was treated with an investigational RNAi therapeutic, revusiran, which targets hepatic transthyretin production. Sixteen months into treatment, he developed bilateral lower-extremity weakness and numbness, worsening balance, difficulty manipulating objects with his hands, and finger numbness. Nerve conduction studies were consistent with multifocal demyelinating neuropathy. Intravenous immunoglobulin therapy improved sensation in his hands and feet, and improved hand dexterity. A sural nerve biopsy demonstrated demyelination with substantial axonal loss in the absence of histologically detectable endoneurial amyloid deposition. This case expands the clinicopathologic spectrum of transthyretin amyloidosis and may represent complex disease and treatment effects.

Key Words: amyloid, neuropathy, sensorimotor, autonomic, RNAi

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INTRODUCTION

Transthyretin amyloidosis (OMIM 105210) is an autosomal dominant, adult-onset, systemic disorder that may present with sensorimotor peripheral neuropathy, autonomic neuropathy, and cardiomyopathy. Approximately 120 mutations in the transthyretin gene have been reported.[1] These predominantly missense mutations lead to the deposition of abnormal, amyloid-forming transthyretin in susceptible tissues.[2] The predilection for peripheral nerve and the mechanisms that subsequently cause nerve damage are not well understood. Most patients with transthyretin amyloidosis show a length-dependent sensorimotor axonopathy and autonomic dysfunction with initial loss of small myelinated fibers and unmyelinated fibers. The polyneuropathy typically is slowly ascending, initially sensory, and symmetrical. Nerve conduction velocity studies first reveal a decrease in sensory nerve action potentials, followed by a decrease in compound muscle action potential (CMAP) with relatively normal conduction velocities (reviewed in Refs. 2 and 3).

The signs and symptoms of peripheral neuropathy may sometimes be present at presentation for patients with the alanine-for-threonine substitution at amino acid 60 (Thr60Ala). This variant was originally described in kindreds from upstate New York and the Appalachian region of the United States[4–6] and has been traced to families with amyloidosis in northwestern Ireland.[7,8] Features of the polyneuropathy that eventually develop include carpal tunnel syndrome and prominent vibration and proprioception deficits. Cardiac involvement and autonomic dysfunction are more common presenting features, resulting in substantial morbidity and mortality.[4,6,7,9,10]

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The first treatment for transthyretin amyloidosis was orthotopic liver transplantation because the vast majority of transthyretin is synthesized in the liver.[11] Many patients, including those with the Thr60Ala mutation, however, have progression of disease after liver transplantation and poor outcomes (reviewed in Refs. 1 and 9), which has prompted consideration of combined heart and liver transplantation for such patients. Therefore, over the past decade, alternative therapies have been explored; for example, tafamidis and diflunisal, each binds to transthyretin homotetramers, thereby preventing dissociation into monomers that may deposit in susceptible tissues. In fact, these 2 drugs have been shown to be efficacious in the early stages of transthyretin amyloidosis (reviewed in Ref. 1). More recent strategies have focused on targeted knockdown of transthyretin with oligonucleotides such as revusiran, inotersen,[12] and patisiran.[13] Revusiran is a double-stranded small interfering RNA (siRNA) directed against transthyretin mRNA and is covalently linked to a moiety that contains 3 N-acetylgalactosamine (GalNAc) sugars to target uptake in the liver. Phase 1[14] and phase 2[15] trials showed up to 92.4% knockdown of serum transthyretin, but development of revusiran was halted when data from a phase 3 study showed increased risk of mortality in those patients treated with revusiran compared with placebo.[16] In this report, we describe a patient with Thr60Ala transthyretin amyloidosis who clinically developed a demyelinating peripheral neuropathy while being treated with revusiran during the open-label phase 2 clinical trial, and discuss the complexity of disease and treatment of amyloid-related neuropathy.

Case Report

A 72-year-old man of Irish descent, diagnosed at age 66 with cardiac amyloidosis with transthyretin Threonine60Alanine mutation (treated with diflunisal), presented with shortness of breath when going upstairs. His family consisted of 3 older brothers who died in their late 60s–70s with chronic heart failure and amyloidosis. Three maternal second cousins were also possibly affected by amyloidosis. There was no clear family history of peripheral neuropathy. He was evaluated for neuropathy 20 months before the start of revusiran treatment trial in April 2013. He did not report paresthesias, fine motor problems, or imbalance. Neurological examination showed mild sensory loss in the legs. An electromyogram/nerve conduction velocity study (EMG/NCVS) suggested a mild sensory neuropathy and bilateral severe median mononeuropathies at the wrists (Table 1).

He started on revusiran in December 2014. Over the next 15 months, he lost 40 pounds, and a delayed gastric emptying study suggested autonomic neuropathy. In addition, he experienced progressive foot numbness and imbalance for 2–3 months. A neurologic examination showed decrease in vibratory sensation in the legs and hands, weakness in the distal hand and great toe extensors, and areflexia in the arms and legs except diminished reflexes in the triceps. He could not stand on his heels and/or his toes, with impaired tandem gait and positive Romberg sign. His NCVS/EMG showed multifocal chronic demyelinating polyneuropathy with evidence of axonal loss in the distal leg, which was not present in the previous study (Table 1). The conduction velocities of all tested nerves and the distal motor latency prolongation of the left fibular, right tibial, left median, and ulnar nerves were in the demyelinating ranges. There was 66% conduction block in the left fibular nerve. There was prolonged distal CMAP duration, indicative of distal temporal dispersion in the left fibular, ulnar, median, and bilateral tibial nerves (duration $\geq$ 9 ms). All sensory responses were absent. Needle EMG of the left arm and leg showed chronic denervation in the distal arm and leg muscles with active denervation in the distal muscles (Table 1). A lumbar puncture showed slightly elevated cerebrospinal fluid protein (54 mg/dL), but cerebrospinal fluid cell count and glucose were within normal limits. He was treated

TABLE 1. Nerve Conduction Velocity Studies and Needle Electromyography

	1 Year and 7 Months Before Starting Revusiran	After 1 Year and 3 Months on Revusiran	After 1 Year and 7 Months on Revusiran and After 4 Months on IVIG
Left median nerve tested at the abductor pollicis brevis			
Distal motor latency (ms)	**6.4**	**16.8**	**17.9**
CMAP amplitude, wrist (mV)	7.5	3.4	0.1
Motor CV, elbow to wrist (m/sec)	53	**35**	34
Temporal dispersion	No	No	No
Distal CMAP duration (ms)	5.2	**9.0**	7.2
Conduction block	No	No	No
F-wave latency (ms)	32.6	**56.4**	No response
Left median sensory nerves			
SNAP amplitude (orthodromic), μV			
Digit II	No response	No response	No response
Digit IV	1	No response	No response
Sensory CV (orthodromic), m/sec			
Digit II	No response	No response	No response
Digit IV	33 L	No response	No response
Left ulnar nerve tested at the abductor digiti minimi			
Distal motor latency (ms)	2.9	4.7	**7.7**
CMAP amplitude, wrist (mV)	8.2	4.7	3.4
Motor CV, below the elbow to the wrist (m/sec)	60	**32**	**20**
Motor CV, above the elbow to below the elbow (m/sec)	58	**13**	**12**
Temporal dispersion distal to proximal stimulation	No	No	No

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TABLE 1. (*Continued*)

	1 Year and 7 Months Before Starting Revusiran	After 1 Year and 3 Months on Revusiran	After 1 Year and 7 Months on Revusiran and After 4 Months on IVIG
Distal CMAP duration (ms)	6.3	**9.9**	8.4
Conduction block	No	Decline of 64% amplitude and 66% area across the elbow	**Decline of 38% amplitude and 31% area in the forearm**, and 62% amplitude and 63% area across the elbow
F-wave latency (ms)	31.1	43.3	**55.0**
Left ulnar sensory nerve			
SNAP amplitude digit V (orthodromic), μV	**3**	No response	No response
Sensory CV (orthodromic), m/sec	50	No response	No response
Left radial sensory nerve			
SNAP amplitude (antidromic), μV	22	No response	No response
Sensory CV (antidromic), m/sec	60	No response	No response
Left fibular nerve tested at the extensor digitorum brevis			
Distal motor latency (ms)	3.9	**9.9**	No response
CMAP amplitude, ankle (mV)	4.2	0.6	No response
CMAP amplitude, fibular head (mV)	3.6	0.2	No response
Motor CV, the fibular head to the ankle (m/sec)	45	**19**	No response
Motor CV, the popliteal fossa to the fibular head (m/sec)	50	20	No response
Temporal dispersion distal to proximal stimulation	No	No	No response

TABLE 1. (*Continued*)

	1 Year and 7 Months Before Starting Revusiran	After 1 Year and 3 Months on Revusiran	After 1 Year and 7 Months on Revusiran and After 4 Months on IVIG
Distal CMAP duration (ms)	6.8	**9.9**	No response
Conduction block	No	**Decline of 66% amplitude and 72% area in the leg segment**	No response
F-wave latency (ms)	45.3	No response	No response
Left superficial fibular nerve			
SNAP amplitude (antidromic), μV	4	No response	No response
Sensory CV (antidromic), m/sec	57	No response	No response
Left tibial nerve at the abductor halluces			
Distal motor latency (ms)	3.9	7.8	No response
CMAP amplitude, ankle (mV)	11	0.5	No response
Motor CV, the popliteal fossa to the ankle (m/sec)	44	**24**	No response
Temporal dispersion distal to proximal stimulation	No	Yes	No response
Distal CMAP duration (ms)	5.3	**20.3**	No response
Conduction block	No	Decline of 41% amplitude and 53% area	No response
F-wave latency (ms)	52.5	No response	No response
Left sural nerve			
SNAP amplitude (antidromic), μV	12	No response	No response
Sensory CV (antidromic), m/sec	52	No response	No response

CV, conduction velocity; SNAP, sensory nerve action potential.
Abnormal measurements are shown in bold.

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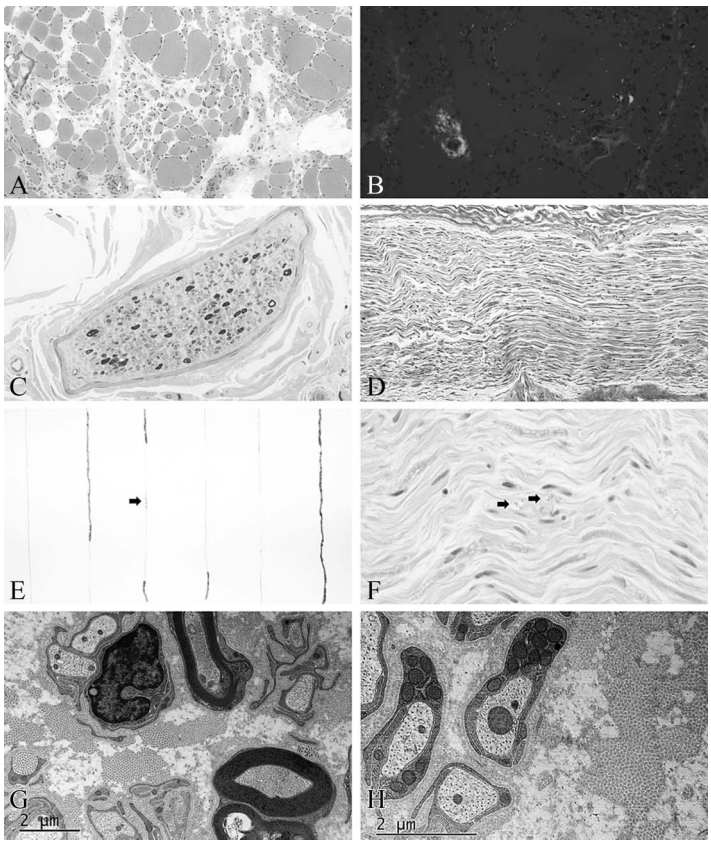

FIGURE 1. Histopathologic features of the gastrocnemius and sural nerve biopsies. A, A low-magnification hematoxylin- and eosin-stained cryosection of the right gastrocnemius biopsy shows numerous variably atrophic myofibers, many of which are clustered or grouped. B, An epifluorescence photomicrograph of the muscle biopsy reveals foci of amyloid deposition, stained with Congo red, within the vascular walls, but not in the endomysium. C, An epoxy thin resin section, of the right sural nerve biopsy, stained with toluidine blue reveals a representative nerve bundle with increased intrafascicular variability. D, A paraffin-embedded, longitudinal section stained with trichrome shows abundant endoneurial fibrosis between relatively sparse nerve fibers. E, A teased fiber preparation shows variable segmental demyelination of many internodes. An arrow denotes myelin debris. F, Myelin debris (arrows) is noted in a longitudinal hematoxylin- and eosin-stained paraffin section. G, An electron micrograph shows a fiber undergoing remyelination (lower left) and numerous large and small caliber axons surrounded by thin, redundant, Schwann cell processes. H, Rare Schwann cells and axons contain enlarged mitochondria.

with intravenous immunoglobulin (IVIG) for his chronic inflammatory demyelinating polyneuropathy–like condition.

Repeat EMG/NCVS 3 months later revealed progression in neuropathy (Table 1). Motor NCVS of the left tibial nerve and left fibular nerve at the extensor digitorum brevis muscle showed no evoked motor response. Distal motor latencies and conduction velocities were in the demyelinating range in the left ulnar nerve and left median nerve. Minimal F-wave latencies were in demyelinating range in the left ulnar nerve. There was prolonged distal CMAP duration, indicative of distal temporal dispersion in the left ulnar nerve (duration $\geq$ 9 ms). There was no sensory evoked response in the left median, ulnar, radial, and sural nerves. EMG of the left leg was performed, which showed active and chronic denervation in the distal leg muscle (Table 1).

He was taken off revusiran in July 2016. He was getting physical therapy for strength and gait training. Three months later, he reported not much change in his symptoms including weakness, imbalance,

and difficulty manipulating objects with his hands. He continued to have numbness in his fingers and distal legs. Neurological examination showed worsening of weakness in extremities (distal > proximal). He was continued on IVIG. Nerve and muscle biopsies were performed.

The right gastrocnemius muscle biopsy showed a neurogenic abnormality including numerous, grouped atrophic fibers (Fig. 1A), composed of type I or type II fibers, with small areas of fiber type grouping (data not shown). In addition, several target fibers were present (data not shown). Amyloid deposits were detected by Congo red (Fig. 1B) and thioflavin S (data not shown) in the intramuscular vascular walls, but not in the endomysium. No inflammation, myonecrosis, regeneration, or other abnormal cytological changes were observed (data not shown).

The right sural nerve biopsy showed a patchy, but overall severe, loss of both large and small myelinated fibers (Fig. 1C). A trichrome stain of a longitudinally sectioned fascicle highlights abundant endoneurial fibrosis (Fig. 1D, blue) interspersed among relatively rare nerve fibers (Fig. 1D, red). Teased fiber analysis revealed segmental demyelination (74.5% of all analyzed fibers), segmental remyelination (21.8%), and myelin wrinkling (1.8%), leaving only 1.8% of the fibers with normal morphology. Wallerian degeneration was not particularly evident (Fig. 1E). Myelin debris (Fig. 1F, arrows) was encountered in the endoneurium, occasionally in the macrophages. Relatively often, thinly myelinated or unmyelinated fibers are seen, many of which are surrounded by thin, elongated Schwann cell processes (Fig. 1G). Although Schwann cell cytoplasmic lamellar or granuloreticular/crystalline inclusions were not revealed by electron microscopy, rare enlarged mitochondria were identified in the axons and Schwann cells (Fig. 1H). Amyloid deposits were detected within the epineurial vascular walls, but not in the endoneurium. Immunofluorescence staining for IgG, IgM, IgA, kappa light chain, lambda light chain, C3d, and C5b-9 showed no pathologic deposition along the nerve sheath. Immunohistochemically, rare CD3(+) T cells were present in the endoneurium and epineurium, but no CD20(+) B cells were detected (data not shown).

Two months later, he reported improvement in handling objects with his hands, in the context of continued treatment with IVIG, with some improved sensation in the extremities. There was no worsening of balance and strength in the extremities. He continued to improve, with improved strength, and was able to return to his job as a handy man. His Rasch-built Overall Disability Scale (R-ODS) improved from 16 to 32, after 16 months of treatment with IVIG.

DISCUSSION

In this report, we describe the clinicopathologic features of a severe demyelinating neuropathy in a patient with Thr60Ala transthyretin amyloidosis treated with revusiran, which might have been relevant, at least in part, to the demyelinating aspect of this neuropathy. In general, the relative contribution of medications may be difficult to tease out in many patients with chronic neuropathy.[17] Our patient's first neurologic evaluation was at age 68, at which time he did not exhibit any notable symptoms of peripheral neuropathy, except for borderline reduction in vibration sense in his toes. He was treated with revusiran for 16 months, and developed markedly impaired gait and decreased sensation in his hands and feet by age 71, when the sural nerve biopsy was performed and showed a chronic and active, severely demyelinating neuropathy with axonal loss.

In our patient's biopsy, no amyloid deposition was histologically detectable in the endoneurium or endomysium (although it was detected in the vessel walls). In general, amyloid is reported to be seen in approximately 90% of nerve biopsies from patients with transthyretin amyloidosis.[18] The pattern of amyloid deposition in the

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biopsied nerve may reflect sampling issues. Alternatively, it may raise the possibility that revusiran treatment itself played a role, independently or combined with progression of the amyloid neuropathy, in the development of demyelination in this particular case. Patients with transthyretin amyloidosis usually present with an axonal polyneuropathy, with occasional segmental demyelination.[2,19,20] Cases of atypical transthyretin-related familial amyloid polyneuropathy in patients with transthyretin mutations, other than Thr60Ala, such as Val30Met, Ser77Thr, Ala91Ser, and Ile107Val have been initially misdiagnosed with chronic inflammatory demyelinating polyneuropathy and typically had 1 or 2 demyelinating findings on nerve conduction studies[3,18,21–24]; however, in their reports, the analyzed nerve biopsies did not show prominent demyelination.[22] Furthermore, a patient with a Val122Ile mutation presented clinically with multifocal demyelinating mononeuropathies, but no evidence of demyelination or remyelination was seen in the sural nerve biopsy from this patient.[25] Our patient, however, had widespread demyelinating findings on electrodiagnostic studies and also improved in neuropathy impairment and function after treatment with IVIG.

Drug-associated demyelinating neuropathies generally can be classified into 2 main categories, based on their proposed mechanism of action: immune mediated and direct toxicity. Tumor necrosis factor–alpha inhibitors, interferon alpha, tacrolimus, and procainamide modulate the immune system. It has been suggested that they may activate T cells or induce an antigen response to cause demyelination (reviewed in Refs. 26 and 27). In our case, however, significant lymphocytic infiltrates were not identified in the nerve biopsy, and immunofluorescence staining for IgG, IgM, IgA, kappa light chain, lambda light chain, C3d, and C5b-9 showed no pathologic deposition along the nerve sheath. On the other hand, amphiphilic drugs such as amiodarone, chloroquine, and perhexiline may cause Schwann cell toxicity in the absence of an immune response (reviewed in Refs. 28 and 29). Characteristic membrane inclusions develop in Schwann cell lysosomes in patients treated with these drugs (reviewed in Ref. 30). Neither lamellar nor granuloreticular/crystalline inclusions were seen in Schwann cells of our patient (Figs. 1C, G, H). The identification of a demyelinating neuropathy associated with bortezomib treatment[31] suggests that additional mechanisms may underlie toxin-induced demyelinating neuropathy. In potential support of a direct effect on the Schwann cell, transthyretin is expressed in Schwann cells.[32,33] Given the mechanism of action of revusiran, several possibilities may be envisioned in this case, including a direct effect of dramatically lowering wild-type transthyretin, off-target transcript silencing, and saturation of the RNA-induced silencing complex, which may impede the silencing of other genes.[34] Alternatively, the GalNAc moieties linked to revusiran may have induced demyelination because Guillain–Barre syndrome has been reported in a subset of patients treated with exogenous gangliosides.[35] The neurologic improvement of patients with patisiran,[13] a similar RNAi that lacks the GalNac label, provides support for this mechanism.

In this report, we have presented a case of demyelinating neuropathy in a patient with a transthyretin-related hereditary amyloidosis treated with revusiran. This severe demyelinating neuropathy may represent an unusual aspect of transthyretin amyloid neuropathy. However, it also raises a question that revusiran treatment could be playing a role, at least in part, in the demyelinating features. Additional studies are needed to elucidate the link between revusiran and demyelinating neuropathy, and its pathomechanism in peripheral demyelination. In vitro experiments and animal models may provide further insight into the mechanisms by which revusiran may modulate myelination.

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