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REVIEW

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The neuropathy in hereditary transthyretin amyloidosis: A narrative review

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Abstract

Hereditary transthyretin amyloidosis (ATTRv) is a condition with adult onset, caused by mutation of the transthyretin (*TTR*) gene and characterized by extracellular deposition of amyloid fibrils in tissue, especially in the peripheral nervous system (PNS) and heart. PNS involvement leads to a rapidly progressive and disabling sensory-motor axonal neuropathy. Although awareness among neurologists increased in recent years thanks to new treatment options, ATTRv is frequently misdiagnosed, and thus a correct diagnosis can be delayed by several years. This review aims to draw the history and features of polyneuropathy in ATTRv based on pathological and electrophysiological correlates. We assessed original articles and case reports based on their relevance to ATTRv neuropathy and we included those appropriate for the scheme of this narrative review. Amyloid fibrils initially deposit in ganglia, causing an axonal neuropathy without amyloid deposits in distal segments (eg, sural nerve biopsy). Over time, amyloid fibrils spread along the nerves, leading to some demyelinating features in the context of severe axonal loss. This review highlights how the features of neuropathy change based on type of ATTRv (early vs late onset) and stage of disease.

KEYWORDS
hereditary transthyretin-mediated amyloidosis, neuropathology, neuropathy, review

1 | INTRODUCTION

Transthyretin (TTR) protein, previously designated as prealbumin, forms a circulating tetramer that is a transport protein for thyroxine and retinol-binding proteins associated with vitamin A.

TTR is present in the serum and cerebrospinal fluid, it is synthetized mostly in the liver, and a small amount is produced by retinal epithelium in the eye and by choroid plexus in the brain.[1]

Mutations in *TTR* gene result in an unstable tetramer that disassociates in misfolded monomers that accumulate in extracellular spaces forming oligomers and ultimately aggregating into amyloid fibrils with the typical structure of cross β-sheets.[2] This conformation allows TTR fibrils to be marked as apple green birefringence deposits under polarized light after Congo red staining.[3] On the other hand, extracellular deposition of TTR-oligomers before fibril aggregation may be visualized using eosinophilic staining and typed by anti-prealbumin antibodies.[4]

Transthyretin-mutated protein accumulates mainly in the heart and the peripheral nervous system (PNS) and to a lesser extent in other organs (eg, brain, kidney, skin, muscle etc.), so hereditary

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transthyretin amyloidosis (ATTRv) is considered a multisystem disorder. Over 130 causative mutations have been identified so far. The most frequent mutation worldwide is Val30Met that in endemic areas (ie, Portugal, Japan, Cyprus) is typically associated with early-onset phenotype (<50 years of age), while in non endemic areas it is associated with late-onset phenotype. The other mutations (namely non-Val30Met) most often exhibit a late-onset phenotype. The initial prevalent involvement of the PNS or heart in ATTRv identifies phenotypes as neurological or cardiac, even though the majority of mutations are associated during the course of disease, with mixed phenotype encompassing the involvement of both systems.[1]

ATTRv polyneuropathy is due to the accumulation of TTR in PNS causing an axonal length-dependent sensory-motor and autonomic neuropathy. ATTRv is a progressive and invalidating neuropathy and, if not treated, ATTRv patients accumulate disability, become wheelchair bound and bedridden, and ultimately die.

The aim of this paper was drawing up the history and features of polyneuropathy in ATTRv based on pathological background.

2 | PATHOLOGICAL BACKGROUND

The characteristic finding in sural nerve biopsies varies based on disease onset: early-onset patients display a prevalent loss of small nerve fibers,[5,6] whereas the fiber loss pattern in late-onset ATTRv is variable, comprising cases with involvement of small nerve fibers and others with prevalent involvement of large caliber fibers and relatively well-preserved small myelinated and unmyelinated fibers.[6-8]

Though the deposition in organs and tissues of TTR amyloid fibrils should represent the feature of ATTRv, actually amyloid deposition finding in nerve biopsy specimens is quite variable and seems to be related to the clinical severity of polyneuropathy.[9] Instead, amyloid deposits are usually found in dorsal root ganglia (DRG) and sympathetic ganglia in both early- and late-onset Val30Met ATTRv. In addition, in early-onset ATTRv the neuronal loss is greater in sympathetic ganglia than DRG, while in late-onset ATTRv cases there is generally an involvement of sensory neurons of all sizes in DRG.[6] No clear evidence of amyloid deposits in DRG was proven yet in non-Val30Met variants.

Additionally, different types of TTR amyloid fibrils distinguish early- from late-onset ATTRv: amyloid fibrils are usually long and thick in early-onset ATTRv, whereas they are short and thin in late-onset ATTRv.[6,10] Importantly, late-onset patients generally display a mixture of full-length and TTR non fibrillar fragments (Type A) while early-onset patients display only full-length TTR fibrils (Type B).[6,11,12] In addition, type amyloid fibrils have a different affinity to Congo red staining. Type A fibrils display a weaker congophilia leading to a poor possibility in detecting amyloid deposition in the biopsies of late-onset patients.

3 | PATHOLOGICAL FEATURES

The pathological findings suggest, well documented in Val30Met variants, that the initial site of amyloid fibrils deposition may be DRG and autonomic ganglia since TTR aggregates are not steadily found in nerve specimens despite the finding of axonal loss due to dying-back degeneration. The greater permeability of blood-nerve barrier proximally[13] might favor the leakage of circulating TTR.

Supporting this, beyond the data from sural nerve biopsies, further evidence comes from skin biopsies that show, in presymptomatic stage of disease, a loss of nerve fibers but none or minimal deposition of amyloid with respect to more advanced stage of ATTRv.[14,15]

Moreover, data from magnetic resonance neurography in ATTRv symptomatic and pre-symptomatic patients confirmed the involvement of the more proximal nerve segments.[16]

Over time, it is expected that TTR deposition may spread along the whole length of peripheral nerves: the TTR accumulation, starting from ganglia and nerve roots (sensory and motor) where the blood-nerve barrier is more permeable, might spread toward the proximal portions of nerves through the physiological proximo-distal gradient of endoneurial fluid.[17,18] However, whether the TTR aggregate accumulation occurs with a proximo-distal gradient, remains to be elucidated.

Anyway, the amyloid deposits, increasing in turn the blood-nerve barrier permeability, might further foster amyloidogenic material deposition and promote spreading along the nerve.[19] Thus, progressive accumulation of amyloid fibrils as well prefibrillar material along the peripheral nerve trunks causes further nerve injury, leading to additional and widespread axonal loss including the large myelinated fibers. Supporting this, the chance to detect amyloid deposits in peripheral nerves seems to be related to disease duration[1,6,20] and consistently, sural nerve findings reveal frequent amyloid deposits and conspicuous axonal loss in the late stage of disease.[1,9,20-22] Moreover, through sural nerve biopsy, at this stage together with axonal loss it is possible to detect myelin abnormalities including nodal gap widening, paranodal myelin retraction as well segmental demyelination. Importantly, myelin alterations are usually in close contact with TTR deposits, suggesting a direct effect of fibrillar and prefibrillar material.[1,8,20-22]

4 | NEURODEGENERATIVE MECHANISMS

The mechanisms underlying neurodegeneration in ATTRv remain largely unknown. Different hypotheses have been put forward. Direct mechanical effect of TTR aggregates on nerve fibers has been proposed since distortion of myelin sheath, segmental demyelination and axonal degeneration were noticed. This effect is typically observed in early-onset patients where the long and thick fibrils invade and become indistinct from basement and cytoplasmic membranes, leading to Schwann cell (SC) atrophy.[23,24] Similarly, the deposition of TTR fibrils occurs in DRG and autonomic ganglia in close association to glial satellite cells that are the equivalent of SCs in peripheral nerves. Furthermore, TTR aggregates might alter axon-SC crosstalk (especially trophic factors), leading to neuronal dysfunction and ultimately cell death.[19] However, it is unlike the hypothesis that neurodegenerative process in ATTRv neuropathy arises solely as the result of mechanical compression by amyloid infiltrates.

An in vitro study showed that non fibrillar TTR aggregates are toxic[25] and are able to induce neuronal inflammatory and oxidative stress, ultimately leading to neuronal death. The toxic effect seems to be the prominent neurodegenerative pathomechanism in late-onset ATTRv patients, in which type A fibrils (mature and pre-fibrillar aggregates) are predominant.[1,6,11,24-28]

Lastly, other mechanisms could be taken into account such as nerve ischemia caused by perivascular amyloids,[26] inefficient cleavage of TTR aggregates[29] and dysfunction of SCs and glial cells.[30]

5 | CLINICAL CORRELATES

Clinical features in ATTRv depend on the types of damaged fibers that in turn depend on the early- or the late-onset phenotype, as well as on early or late stage of disease.

In the early-onset phenotype and at early stage of disease, the preferential loss of small caliber fibers gives rise to symptoms of small fiber neuropathy that represents the earliest clinical feature. Patients notice primarily pain and thermal sensation dysfunction and dysautonomia including gastrointestinal, cardiovascular, sexual and sweating disturbances. Neuropathic symptoms typically begin in the feet and later extend proximally following a pattern of disto-proximal axonal degeneration.[1] Early occurrence of autonomic impairment in patients with somatic peripheral neuropathy represents for clinicians a red flag that may create a suspicion for ATTRv, especially in an endemic area.[31] The progression of amyloid deposits along the entire length of the nerve leads to a widespread involvement of nerve fibers including those of large caliber, both sensory and motor. Indeed, large fiber peripheral neuropathy progresses in early-onset ATTRv and patients accumulate disability over time, moving from FAP1 stage (sensory polyneuropathy that leads to difficulty walking without assistance), to FAP2 stage (sensorimotor polyneuropathy that necessitates assistance for walking), to FAP3 stage (wheelchair bound or bedridden) of disease and ultimately die within about 12 years of disease onset.[1]

Conversely in late-onset ATTRv, perhaps for a different underlying pathomechanism (ie, toxic effect), preferential involvement of the small nerve fibers as an early clinical feature is not typical.[31] Actually, in the late-onset ATTRv, the clinical picture is characterized by early impairment of the largest nerve fibers that usually overwhelms the small nerve fiber involvement. Typically, patients exhibit sensory and motor involvement together with gait difficulties, and autonomic dysfunction is often scarcely clinically relevant and remains under-recognized if not properly investigated. Symptoms of autonomic neuropathy usually include erectile dysfunction, alternating diarrhea and constipation, and postural hypotension. Certainly, the occurrence of dysautonomia in the context of an idiopathic polyneuropathy must hint toward amyloidotic neuropathy even in late-onset patients.

As for early-onset ATTRv, neuropathy invariably progresses in late-onset ATTRv as well,[32,33] where the natural history of the late-onset ATTRv is characterized by a rapid course and survival is around 7 years from disease onset[32-35] and a worse prognosis is associated with cardiac involvement.[35,36]

Importantly, late-onset ATTRv, once clinically manifested, worsens faster than the early-onset phenotype and the other peripheral neuropathies considered for the differential diagnosis are chronic inflammatory demyelinating polyneuropathy (CIDP), diabetic neuropathy and Charcot-Marie-Tooth disease.[6,37,38] Thus, a rapid progressive course represents a relevant clinical red flag for raising the suspicion for ATTRv neuropathy, in particular in late-onset phenotype.[1]

6 | ELECTROPHYSIOLOGICAL CORRELATES AND DIFFERENTIAL DIAGNOSES

Overall, it is given that peripheral neuropathy in ATTRv is a progressive axonal and length-dependent sensory-motor and autonomic neuropathy.[39]

However, electrophysiological features as well as clinical picture depend on type of ATTRv (early- vs late-onset) and on the time when neurophysiological study is performed. This is required in order to properly interpret electrophysiological results.

In early stage of early onset ATTRv, small nerve fiber involvement is clinically relevant and nerve conduction study (NCS) may be normal. Thus, it is important to assess small fiber neuropathy (SFN) using quantitative sensory test, laser-evoked potentials, contact heat evoked potentials, sympathetic skin response, Sudoscan, cardiovascular reflex and skin biopsy.[40] At this stage, other causes of SFN should be considered in differential diagnosis.[40] Over time in early-onset ATTRv patients, the initial small fiber neuropathy progresses to the involvement of larger fibers and NCS may demonstrate a sensory-motor neuropathy.

Conversely, in late-onset ATTRv, the large fiber involvement is generally more evident and small fiber symptoms can be absent or subclinical. NCS discloses a predominantly sensory or sensory-motor axonal distal symmetric polyneuropathy. At this stage, differential diagnosis with other axonal neuropathies including diabetic, renal insufficiency, genetic (ie, Charcot-Marie-Tooth) or idiopathic[37] is challenging for clinicians. Dysautonomic disturbances as well bilateral CTS may represent red flags to cause suspicion for ATTRv.

Over time, amyloid deposits are spread along the PNS and axonal loss progressively increases and demyelinating features may also occur. Thus, at a later stage NCS may reveal slow reduction in nerve conduction velocity (NCV) in the range of demyelination so that the most frequent misdiagnosis is CIDP.[38] However, while CIDP is a primary demyelinating disorder, NCV slowing in ATTRv patients is always associated with marked reduction in motor and sensory action potential amplitudes.[41] Unresponsiveness to immunomodulatory treatment may also be useful in differentiating TTR from CIDP, which is rapidly progressive.

More challenging may be differential diagnosis with hematological diseases such as amyloidosis or POEMS (polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy and skin lesions) syndrome that have a progressive course and predominantly axonal features combined with demyelination.

7 | CONCLUSIONS

Neuropathy is a hallmark of ATTRv, representing one of the most disabling and progressive condition. However, the neuropathy in ATTRv is often not correctly interpreted, leading to frequent misdiagnosis, especially in late-onset patients as they usually present as sporadic cases. It is important to note that the features of neuropathy are not always the same and they change depending on both type of ATTRv (early vs late onset) and stage of disease. Indeed, though ATTRv neuropathy is a primary axonal neuropathy it may change over time from a pure axonal to a mixed (axonal and demyelinating) neuropathy, making the diagnosis more challenging.

CONFLICT OF INTEREST

The authors declare no potential conflict of interest.

AUTHOR CONTRIBUTIONS

Stefano Tozza and Fiore Manganelli had a major role in conception, design and drafting the work; Daniele Severi, Emanuele Spina, Aniello Iovino and Francesco Aruta collected data for the work; Lucia Ruggiero, Raffaele Dubbioso, Rosa Iodice and Maria Nolano interpreted the data. All authors had an important role in critically revising the work and approved the final version to be published.

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