REVIEW

"Red-flag" symptom clusters in transthyretin familial amyloid polyneuropathy

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Abstract Transthyretin familial amyloid polyneuropathy (TTR-FAP) is a rare, progressive, life-threatening, hereditary disorder caused by mutations in the transthyretin gene and characterized by extracellular deposition of transthyretin-derived amyloid fibrils in peripheral and autonomic nerves, heart, and other organs. TTR-FAP is frequently diagnosed late because the disease is difficult to recognize due to phenotypic heterogeneity. Based on published literature and expert opinion, symptom clusters suggesting TTR-FAP are reviewed, and practical guidance to facilitate earlier diagnosis is provided. TTR-FAP should be suspected if progressive peripheral sensory-motor neuropathy is observed in combination with one or more of the following: family history of a neuropathy, autonomic dysfunction, cardiac hypertrophy, gastrointestinal problems, inexplicable weight loss, carpal tunnel syndrome, renal impairment, or ocular involvement. If TTR-FAP is suspected, transthyretin genotyping, confirmation of amyloid in tissue biopsy, large- and small-fiber assessment by nerve conduction studies and autonomic system evaluations, and cardiac testing should be performed.

Key words: diagnosis, hereditary amyloidosis, transthyretin, transthyretin familial amyloid neuropathy

Introduction

Transthyretin familial amyloid polyneuropathy (TTR-FAP) is an autosomal-dominant, adult-onset disorder associated with over 100 different mutations in the transthyretin (*TTR*) gene that cause transthyretin protein to deposit as amyloid in peripheral and autonomic nerves, heart, gastrointestinal (GI) tract, kidneys, eyes, and connective tissue of the transversal carpal ligament *(Ando et al., 2013; Rowczenio et al., 2014; Sekijima, 2015)*. This results in progressive organ dysfunction and death within an average of 10 years *(Ando et al., 2013)*.

TTR-FAP is a highly heterogeneous disease associated with a wide range of clinical manifestations that may present in varying degrees and combinations *(Ando et al., 2013; Sekijima, 2015)*. It is frequently dominated by progressive and relentless peripheral nerve damage. The disease can be difficult to recognize due to its variable clinical presentation and non-specific symptoms. The age of onset ranges from the second to ninth decade of life *(Ando et al., 2013)*, and incomplete penetrance of clinical disease can lead

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to sporadic cases without known affected relatives. Accurate diagnosis of TTR-FAP is often delayed for years *(Planté-Bordeneuve et al., 2007; Koike et al., 2011; Dohrn et al., 2013; Adams et al., 2014)*. Making an accurate diagnosis is important to permit effective disease management, as tissue damage is largely irreversible, and available treatment options are most beneficial in early disease stages *(Coelho et al., 2013; Planté-Bordeneuve, 2014; Ericzon et al., 2015)*. This perspective provides practical guidance on early detection of TTR-FAP.

Clinical Features of TTR-FAP

Typical clinical symptoms associated with TTR-FAP are illustrated in Fig. 1. A particular challenge in making a diagnosis is that clinical manifestations are not necessarily uniform among carriers of the same *TTR* mutation and can vary even within the same family *(Ando et al., 2013)*. The clinical phenotype is also influenced by genetic, epigenetic, or environmental factors other than the *TTR* mutation (see Table 1). The pattern of amyloid deposition may also play a role *(Bergström et al., 2005; Ihse et al., 2013)*.

Length-dependent peripheral sensory-motor neuropathy is a hallmark feature of TTR-FAP. In classical early-onset (<50 years of age) Val30Met TTR-FAP *(Andrade, 1952)*, distal small myelinated and unmyelinated nerve fibers associated with pain and temperature sensation become damaged first, which may manifest as paresthesia, dysesthesia, allodynia, hyperalgesia, or spontaneous pain in the feet. Axonal degeneration then progresses relentlessly in a distal to proximal pattern reaching upper limbs usually 4 to 5 years after first symptoms. Within a few years, larger myelinated sensory and motor nerve fibers become affected and impairment of light touch, vibration, and position sensation, and motor deficit appear in the distal lower limbs. Motor deficits also follow a length-dependent progression, causing increasing walking difficulty and weakness.

Late-onset cases are characterized by relative preservation of unmyelinated nerve fibers and conspicuous presence of axonal sprouting *(Koike et al., 2004)*. These characteristics are responsible for impaired superficial and deep sensation, severe neuropathic pain, early distal motor involvement, and relatively mild autonomic symptoms *(Conceição and De Carvalho, 2007; Koike et al., 2011)*.

Common Diagnostic Pitfalls

The length-dependent pattern of symmetric sensory-motor and autonomic polyneuropathy in

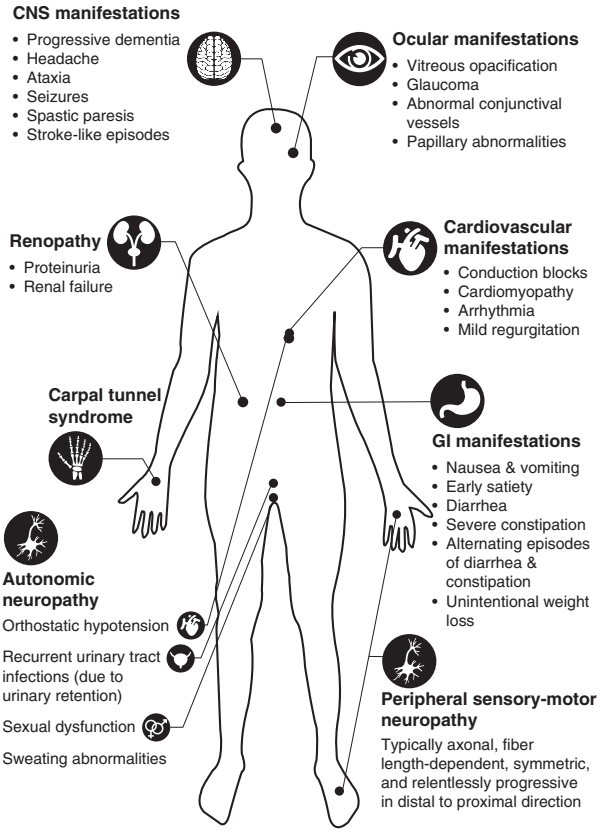

Figure 1. Clinical features associated with TTR-FAP. CNS, central nervous system; GI, gastrointestinal.

TTR-FAP is not unique, and similar neurologic impairments can be observed in many conditions, all of which can mislead clinical diagnosis.

The most common neuropathic misdiagnosis for sporadic TTR-FAP is chronic inflammatory demyelinating polyneuropathy (CIDP) *(Planté-Bordeneuve, 2014)*. For instance, 20% of 90 French patients without a family history of TTR-FAP *(Planté-Bordeneuve et al., 2007)* and 53% of 15 Japanese patients with sporadic V30M TTR-FAP *(Koike et al., 2011)* were initially misdiagnosed with CIDP. Although CIDP is generally characterized by a demyelinating sensory-motor neuropathy, once extensive axonal length-dependent damage is present, electrophysiological characteristics of TTR-FAP can resemble those of CIDP due to secondary demyelination. Furthermore, protein levels in cerebrospinal fluid can be elevated in patients with TTR-FAP, albeit less markedly than in CIDP. In some cases, a negative biopsy contributed to misdiagnosis. Given the frequent misdiagnosis, there should be a high suspicion index for TTR-FAP in patients diagnosed with CIDP that do not respond to immunomodulatory treatment.

There have been numerous cases where TTR-related amyloidosis was initially misdiagnosed

Table 1. Initial symptoms of TTR-FAP.

	(Coutinho et al., 1980)	*(Conceição and De Carvalho, 2007)*		*(Koike et al., 2002)*		*(Planté-Bordeneuve et al., 1998)*		*(González-Duarte et al., 2013)*
	Portugal	Portugal		Japan		France		Mexico
	n = 483	*n* = 43	*n* = 43	*n* = 82	*n* = 59	*n* = 30	*n* = 35	*n* = 58
	Val30Met	Early-onset Val30Met*	Late-onset Val30Met†	Early-onset Val30Met*	Late-onset Val30Met†	Val30Met	Non-Val30Met	Ser50Arg, Ser52Pro, or Gly47Ala
Age of onset, years, mean (SD)	Men 31 Women 33	33.1 (5.4)	59.5 (6.8)	31.9 (7.6)	62.5 (6.2)	51.3 (15.6)	56.9 (10.6)	35 (11.0)
Symptoms, % of patients‡								
Sensory-motor symptoms	45.4%	35%	84%	57%	81%	60%	82%	51%
Autonomic and GI symptoms	GI symptoms 40.4% Impotence 5.8%§	65%	16%	48%	10%	35%	9%	Diarrhea or constipation 12% Orthostatic hypotension 3% Urinary retention 1%¶
Neuropathic pain	4.8%	2%	47%	–	–	–	–	–
Plantar ulcers	5.2%	–	–	–	–	–	–	–
Weight loss	15.1%	–	–	5%	0%	0%	5%	–
Fatigability	8.3%	–	–	–	–	–	–	–
Cardiac signs	–	0%	14%	0%	5%	5%	5%	–
Renal dysfunction	–	0%	7%	–	–	–	–	–
Ocular symptoms	–	0%	2%	0%	2%	–	–	–

GI, gastrointestinal; TTR-FAP, transthyretin familial amyloid polyneuropathy; SD, standard deviation.
*Less than 50 years of age at symptomatic disease onset.
†At least 50 years of age at symptomatic disease onset.
‡Patients may have more than one first symptom.
§A total of 8.9% of males.
¶Urinary retention might be underdiagnosed as patients are usually not aware or cognisant of symptoms.

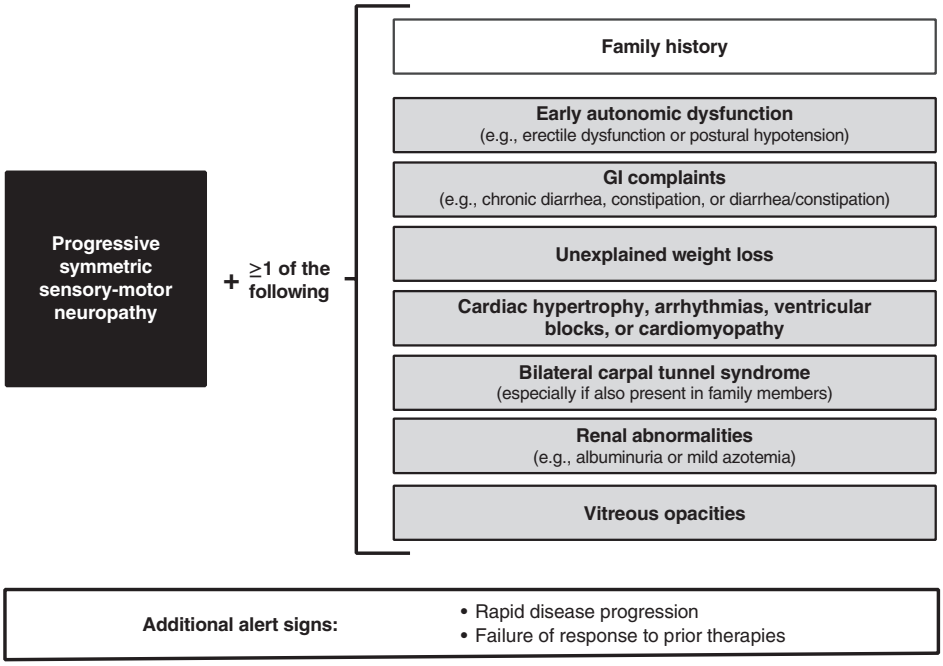

Figure 2. Potential "red-flag" symptom clusters that may warn of a diagnosis of transthyretin familial amyloid polyneuropathy (TTR-FAP).

as amyloid light-chain (AL) amyloidosis *(Cowan et al., 2011; Briani et al., 2012)*. Misdiagnosis can be due to occurrence of monoclonal gammopathy in elderly patients or false immunolabeling of amyloid deposits, leading to inappropriate, potentially harmful chemotherapeutic treatment. This can be avoided by careful typing of the amyloid precursor protein.

TTR-FAP is unlikely to be mistaken for other forms of hereditary amyloid neuropathy caused by mutation of the apolipoprotein A-I, gelsolin, or β_2-microglobulin genes. However, although very rare and less rapidly progressive, hereditary neuropathy due to truncation mutations of the prion protein can closely mimic TTR-FAP *(Mead and Reilly, 2015)* and should be considered in the differential diagnosis.

"Red-flag" Symptom Combinations That May Warn of a Diagnosis of TTR-FAP

Characteristic features that can help identify TTR-FAP are heritability and general multi-symptom involvement. Consequently, it is important to obtain a complete clinical history with details of symptoms of systemic disease and a complete and detailed family history *(Ando et al., 2013; Planté-Bordeneuve, 2014)*. The occurrence of progressive peripheral sensory-motor polyneuropathy and at least one of the following is suggestive of TTR-FAP: family history of neuropathy, early autonomic dysfunction, cardiac involvement, diarrhea, constipation, alternating episodes of constipation and diarrhea, inexplicable weight loss, carpal tunnel syndrome, renal impairment, or vitreous opacity (Fig. 2).

Of these combinations, peripheral neuropathy with early autonomic signs, such as erectile dysfunction or GI symptoms, and peripheral neuropathy with cardiac manifestations are the most common and important combinations in sporadic patients. Rapid disease progression *(Dohrn et al., 2013)* and failure to respond to immunomodulatory treatment are additional signs.

Core Diagnostic Tests to Identify TTR-FAP

The clusters of clinical symptoms mentioned above should raise suspicion of TTR-FAP, particularly if there is a positive family history. In patients with suspected TTR-FAP, *TTR* genotyping should be performed. In sporadic cases, the entire coding region of the *TTR* gene, that is all four exons, should be sequenced. Tissue biopsy analysis and neurologic, cardiac, autonomic, and ophthalmologic evaluation can lend further credence to the correct diagnosis.

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