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Guideline of transthyretin-related hereditary amyloidosis for clinicians

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Abstract

Transthyretin amyloidosis is a progressive and eventually fatal disease primarily characterized by sensory, motor, and autonomic neuropathy and/or cardiomyopathy. Given its phenotypic unpredictability and variability, transthyretin amyloidosis can be difficult to recognize and manage. Misdiagnosis is common, and patients may wait several years before accurate diagnosis, risking additional significant irreversible deterioration. This article aims to help physicians better understand transthyretin amyloidosis—and, specifically, familial amyloidotic polyneuropathy—so they can recognize and manage the disease more easily and discuss it with their patients. We provide guidance on making a definitive diagnosis, explain methods for disease staging and evaluation of disease progression, and discuss symptom mitigation and treatment strategies, including liver transplant and several pharmacotherapies that have shown promise in clinical trials.

Keywords: Amyloidosis, Polyneuropathy, Cardiomyopathy, Oculoleptomeningeal, Transthyretin, Liver transplant, Genetics

Introduction

Transthyretin (TTR) amyloidosis is a systemic disorder characterized by the extracellular deposition of amyloid fibrils composed of TTR, a plasma transport protein for thyroxine and vitamin A that is produced predominantly by the liver. TTR can dissociate from its native tetramer form, then misfold and aggregate into amyloid fibrils that accumulate in various organs and tissues, causing progressive dysfunction. TTR amyloidosis is the most common form of hereditary (familial) amyloidosis, and is caused by mutations that destabilize the TTR protein. TTR amyloidosis also encompasses an age-related amyloidosis known as senile systemic amyloidosis, an acquired disorder mainly affecting men after the age of 60 years, that results from the deposition of wild-type TTR amyloid.

TTR amyloidosis can present as a progressive, axonal sensory autonomic and motor neuropathy (familial amyloidotic polyneuropathy; TTR-FAP, also known as FAP or ATTR-PN) or as an infiltrative cardiomyopathy (familial amyloid cardiomyopathy). TTR amyloidosis, including TTR-FAP, presents in many different forms, with considerable phenotypic variation across individuals and geographic locations. Diagnosis can be challenging and treatment often requires a multidisciplinary approach. Physicians likely to diagnose and treat patients with this disease include neurologists, cardiologists, gastroenterologists, ophthalmologists, and other specialists.

The recommendations offered here, which focus primarily on the management of polyneuropathy symptoms, are based on the published literature, information gleaned from the Transthyretin Amyloidosis Outcomes Survey (THAOS) – a TTR amyloidosis patient registry, and the opinions of the authors. To further assist the treating physician, Appendix A contains lists of recommended reading and helpful websites.

Background

In 1952 Andrade reported a large group of patients in Portugal who had TTR-FAP with the Val30Met *TTR* mutation [1]. Over the next two decades other large foci were discovered in Japan and Sweden. Initially, TTR-FAP was thought to be restricted to endemic occurrences in those areas. However, owing to progress in bioche

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mical and molecular genetic analyses, TTR-FAP is now diagnosed worldwide. Most cases involve small kindreds or patients with no family history of the disease. To date, about 120 different single or double mutations, or a deletion in the *TTR* gene, have been reported; the majority of these *TTR* mutations are amyloidogenic, with fewer than ten considered non-pathogenic [2,3]. Val30Met is the most common mutation and the only one found in large foci of patients.

Some mutations induce cardiomyopathy as the predominant feature (e.g. Val122Ile, Ile68Leu, Thr60Ala, Leu111Met) while others are associated primarily with neuropathy (e.g. Val30Met), but both manifestations can be present in different proportions [4]. Less common disease signs include vitreous opacities, renal disease, and meningeal involvement. While genotype and population origin are important determinants of symptoms, the clinical picture of an affected individual may deteriorate over time (as amyloid continues to deposit in other tissues), and variability may be observed within the same family.

Genetics

TTR-FAP has autosomal dominant inheritance with variable penetrance. Carriers of the mutation have a circulating variant protein from fetal life but no amyloid deposition or symptomatic disease until adulthood, with development of disease probably controlled by factors associated with the biochemistry of aging [3,5]. The penetrance of the gene varies in different regions of the world and among families [6-8]. There is some evidence that affected women transmit higher disease penetrance to their offspring than affected men [9]. Because penetrance is incomplete, carriers of the gene may live to an advanced age without symptoms of the disease but may see their children become clinically affected. Genetic anticipation (earlier onset with greater severity in subsequent generations) has been observed in endemic regions [6,10-12].

Prevalence and age at onset of TTR amyloidosis

Val30Met is the most prevalent TTR-FAP mutation in the world, focused in Portugal, Sweden, Japan, Brazil, and Majorca, and is believed to have arisen independently in Portugal and Sweden [13-15]. The largest cluster of individuals with TTR-FAP caused by the Val30Met mutation may be found in northern Portugal (Póvoa de Varzim and Vila do Conde), where the incidence is estimated to be one in 538 individuals [16]. In contrast, the incidence of hereditary TTR amyloidosis in the United States is estimated to be one in 100,000 individuals [17]. The cardiomyopathy-related Leu111Met and Val122Ile mutations are found primarily in Danish and African American populations, respectively. However, all mutations, including Val30Met, are identified across all countries in different families without any obvious relationship.

In Europe, the prevalence of TTR-FAP is estimated to be less than one in 100,000 individuals [18]. In endemic areas of northern Sweden (Piteå and Skellefteå), the frequency of the Val30Met mutation is 4%; however, the penetrance is relatively low (11% by 50 years) [6]. Conversely, in Portugal, the penetrance is high (80% by 50 years) [7]. Although also endemic in some areas of Japan, the prevalence of TTR-FAP is estimated to be lower than in Europe, at approximately one in 1,000,000 individuals [19].

The frequency of the Val122Ile mutation in the African American population is 3% to 3.9% [20,21], with most individuals developing late-onset cardiac amyloidosis. The frequency of Val122Ile in Caucasian and Hispanic populations in the United States is 0.44% and 0%, respectively [21]. The worldwide prevalence of TTR amyloidosis dominated by cardiomyopathy is unknown, but it is almost certainly underdiagnosed, particularly in the African American Val122Ile carrier population older than 65 years (approximately 135,000 individuals) [22,23].

The age at onset of disease-related symptoms varies between the second and ninth decades of life, with great variations across different populations. Expected age at onset is critical to determine when amyloidosis testing should be requisitioned. Portuguese and Japanese foci of patients with TTR-FAP have traditionally been described as early-onset (mean age, 33 years) [24,25], whereas Swedish patients with TTR-FAP are characterized by a later mean age of onset (56 years) [26]. Even in foci generally considered early-onset, some subgroups of patients experience a later onset. In Japan, especially, a form of later-onset TTR-FAP with no genealogical relationship to the two foci of this disease now predominates [24,27]. Patients with cardiomyopathy who have wild-type or variant *TTR* traditionally develop symptoms in their sixties.

The mean duration of disease onset to death is approximately 10 years but may vary depending on endemic region, genotype, symptoms, and other factors.

Clinical presentation of TTR amyloidosis with polyneuropathy (TTR-FAP)

TTR-FAP is a multi-symptom disease that may present with peripheral neuropathy (sensory and motor), autonomic neuropathy, gastrointestinal impairment, cardiomyopathy, nephropathy, or ocular deposition. While the symptoms described below, including those of Val30Met TTR-FAP patients, may be present in patients with different TTR-FAP genotypes, phenotypes are not always uniform, and the same point mutation may have varied phenotypes even within the same family. Generally, however, most TTR-FAP cases are classified as neuropathic.

Variation in neuropathies of Val30Met TTR-FAP

The clinical picture for Val30Met TTR-FAP differs considerably between patients originating from endemic foci and patients with non-endemic origins [28]. In the former, disease onset often occurs before the age of 40 years, with a progressive sensory-motor and autonomic neuropathy, eventually causing cachexia and death 10 to 20 years after onset. Although sensory and motor manifestations are generally the presenting symptoms, the first clinical presentation can be autonomic neuropathy. However, even when the disease starts with sensory neuropathy, autonomic neuropathies often follow [29]. Patients with Val30Met TTR-FAP and non-endemic origins typically have onset at a late age (usually after the age of 60), with male predominance and an apparently sporadic disease presentation. Sensory and motor neuropathy symptoms of both upper and lower extremities may appear within a short period or even simultaneously, while autonomic neuropathies may be relatively mild [30-32].

Peripheral nerve dysfunction

TTR amyloidosis induces a length-dependent peripheral neuropathy. Initially the lower limbs are affected, and symptoms generally include toe discomfort such as numbness and spontaneous pain. At this stage, as amyloid typically first affects small nerve fibers altering pain and temperature sensation, clinical examination may detect impaired thermal sensitivity in the feet, with decreased pinprick sensation. In contrast, light touch may be relatively preserved and proprioception spared. Muscle strength and tendon reflexes are normal. This neuropathic manifestation typically reflects the involvement of unmyelinated and small myelinated fibers. A few months later sensory loss extends above the ankle on both sides. The neurologic deficit then progresses relentlessly, with the extension of sensory loss toward the proximal lower limbs. Motor deficit appears in the distal lower limbs, as does the impairment of light touch and deep sensations, which indicates the involvement of larger sensory and motor nerve fibers. Walking becomes increasingly difficult with loss of balance and steppage gait. Neuropathic pain is often of the burning type and is worse at night and associated with allodynia. As months and years pass, sensory deficit extends to the thighs, then the upper limbs, forearms, and fingers as the anterior trunk is involved. Motor deficits also follow a length-dependent progression and walking without assistance becomes increasingly difficult. Life-threatening autonomic dysfunction is generally present at this stage along with weight loss and muscle wasting. Loss of pain sensation with preservation of strength leads to painless trauma and the development of plantar ulcers and foot osteoarthropathy (Charcot's joints) [33]. Due to the random distribution of amyloid in the peripheral nervous system, deposits may accumulate locally and induce focal deficit of a cranial nerve, nerve trunk, or plexus. Carpal tunnel syndrome is an early but nonspecific manifestation of TTR-FAP. It should be noted that many patients with TTR-FAP are erroneously diagnosed with simple carpal tunnel syndrome; progressive symptoms or lack of improvement after carpal tunnel release surgery often leads to the correct diagnosis.

In patients who have peripheral neuropathy of unknown origin, testing for autonomic dysfunction should be considered because patients may not show overt symptoms of autonomic failure. Early recognition of autonomic failure may lead to an earlier diagnosis of the underlying pathogenesis of amyloidosis [34].

Other system involvement

Autonomic nervous system involvement includes anhidrosis, sexual impotence, disturbances of gastrointestinal motility (most commonly diarrhea alternating with constipation, but also constipation, diarrhea, nausea, and vomiting), orthostatic hypotension, and neurogenic bladder. In our experience, cardiac disease occurs in approximately 50% of patients with TTR-FAP, with most *TTR* mutations causing amyloid cardiomyopathy [35]. Anemia due to low erythropoietin levels also may be observed [36]. Ocular involvement, such as vitreous opacity, dry eye, glaucoma, and pupillary disorders, is common [37]. In contrast, kidney involvement is unusual.

Additional symptoms of TTR-FAP include hoarseness, coldness, decreased skin temperature, dyscoria, dysesthesia, muscle weakness and atrophy, dissociated anesthesia, and constitutional conditions such as weight loss, arrhythmia, edema, and burning.

When should a neurologist suspect TTR-FAP?

It is important to differentiate a diagnostic process in individuals with a known amyloid family history, especially in endemic areas, from that in patients without such a history (Table 1). In patients with a known family history of TTR-FAP, the onset of symptoms and signs of peripheral neuropathy, manifestations of autonomic dysfunction, and cardiac arrhythmia call for confirmation of the involvement of these organs by appropriate investigations (see Tests and Assessments, below). When there is no known family history of amyloidosis, the diagnosis of TTR-FAP should be considered in patients with a progressive, length-dependent axonal polyneuropathy predominantly affecting temperature and pain sensation. Special attention must be paid to patients with concurrent autonomic dysfunction, cardiac involvement, and carpal tunnel syndrome.

The multisystem involvement of TTR-FAP is a clue to the diagnosis. It is important to consider the diagnosis