Familial amyloid polyneuropathy

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Familial amyloid polyneuropathies (FAPs) are a group of life-threatening multisystem disorders transmitted as an autosomal dominant trait. Nerve lesions are induced by deposits of amyloid fibrils, most commonly due to mutated transthyretin (TTR). Less often the precursor of amyloidosis is mutant apolipoprotein A-1 or gelsolin. The first identified cause of FAP—the TTR Val30Met mutation—is still the most common of more than 100 amyloidogenic point mutations identified worldwide. The penetrance and age at onset of FAP among people carrying the same mutation vary between countries. The symptomatology and clinical course of FAP can be highly variable. TTR FAP typically causes a nerve length-dependent polyneuropathy that starts in the feet with loss of temperature and pain sensations, along with life-threatening autonomic dysfunction leading to cachexia and death within 10 years on average. TTR is synthesised mainly in the liver, and liver transplantation seems to have a favourable effect on the course of neuropathy, but not on cardiac or eye lesions. Oral administration of tafamidis meglumine, which prevents misfolding and deposition of mutated TTR, is under evaluation in patients with TTR FAP. In future, patients with FAP might benefit from gene therapy; however, genetic counselling is recommended for the prevention of all types of FAP.

Introduction

Amyloidoses are a group of diseases characterised by tissue deposition of insoluble proteins and fibril aggregates oriented in a β-pleated sheet structure that form unbranched amyloid fibrils of 10–12 nm diameter. Amyloidosis can be acquired or hereditary. There are three main types of familial amyloid polyneuropathy (FAP), defined according to the precursor protein of amyloid: transthyretin (TTR), apolipoprotein A-1, and gelsolin. The main features of each type of FAP, and current approaches to diagnosis and treatment, are shown in the table.

TTR FAP is a life-threatening disease transmitted as an autosomal dominant trait. Nerve lesions are induced by deposits of fibril protein caused by mutated TTR (mTTR). TTR FAP typically causes a nerve length-dependent polyneuropathy that starts in the feet with loss of temperature and pain sensations, with autonomic dysfunction leading to death within 10 years on average. Apoliprotein A-1 amyloidosis, also known as the Iowa type, is characterised by the deposition of amyloid in major organs, including the kidneys, liver, and heart. Although a nerve length-dependent polyneuropathy can occur in apolipoprotein A-1 FAP, it is not a prominent feature of the disease. Gelsolin amyloidosis is characterised by cranial and peripheral sensory neuropathy, corneal lattice dystrophy, and cutis laxa. The course of gelsolin amyloid neuropathy is slow and quite benign.

In this Review, we describe the clinical manifestations and recent progress in the genetics and treatment of FAP, with special emphasis on TTR amyloidosis, which is by far the most common and devastating disease in this group.

TTR amyloidosis

Andrade first described FAP in north Portugal in 1952.[1] The disease was subsequently reported in Japan (1968)[2] and Sweden (1976).[3] TTR was identified as the precursor of amyloid in this setting, and was found to be synthesised mainly by the liver.[4] The most common pathogenic substitution, Val30Met, was then described and the *TTR* gene was fully sequenced in 1985.[5] In 1990, liver transplantation was undertaken as a therapeutic approach for the treatment of FAP for the first time.[6]

Two main patterns of sensory-motor deficit occur in patients with TTR FAP, both of which are associated with variable autonomic disturbance and extra-neurological manifestations. The most common sensory-motor deficit is nerve length-dependent sensory-motor polyneuropathy; the other type starts with focal deficits resulting from local deposits of amyloid. The pattern and pace of the neurological deficit varies between patients. Some patients with an early-onset presentation deteriorate quickly because of autonomic dysfunction and rapid progression of the sensory-motor deficit. Conversely, in many patients with a late-onset FAP, the polyneuropathy progresses slowly, often with cardiac involvement but with less autonomic dysfunction (figure 1). In other populations, cardiac manifestations are the most prominent symptom, and there is little neurological deficit.

Sensory-motor neuropathy

Length-dependent sensory-motor polyneuropathy

In Portugal, the first symptoms of this pattern of polyneuropathy typically occur in adult patients in their mid-30s; symptom onset is later in Sweden and France. Symptoms start with discomfort in the feet, including numbness and spontaneous pains. At this stage, clinical examination can already detect impaired thermal sensibility over the feet, with decreased pin-prick sensation. However, light touch sensation and proprioception are preserved. Muscle strength and tendon reflexes are normal. This neurological defect typically points to involvement of unmyelinated and small myelinated fibres.[7–9]

A few months after symptom onset, sensory loss has extended above the ankle level on both sides, with

	Transthyretin FAP	Apolipoprotein A-1 FAP	Gelsolin FAP
Geographic distribution	Endemic in Portugal, Sweden and Japan; sporadic presentation worldwide Several thousand cases worldwide	Rare cases	Most cases in Finland (400 cases) but occasional cases worldwide
Transmission	Autosomal dominant	Autosomal dominant	Autosomal dominant
Age at onset	Early onset: third to fourth decade Late onset: sixth to eighth decade	Fourth to fifth decade	Third to fourth decade
Main clinical features	Length-dependent small-fibre sensory-motor polyneuropathy with life-threatening autonomic dysfunction Frequent cardiac and eye involvement	Kidneys, liver, and gastrointestinal tract affected, often leading to organ failure	Corneal lattice dystrophy, cranial neuropathy, and cutis laxa
Diagnosis in familial cases	Family history DNA testing: >100 mutations in *TTR* gene	Family history DNA testing: 16 mutations in *APOA1* gene	Family history DNA testing: one mutation accounts for most cases, another one is extremely rare
Diagnosis in sporadic cases	Amyloid deposits in tissues, identified by nerve biopsy or biopsy of salivary glands or abdominal fat Identification of amyloid type by immunolabelling or mass-spectroscopy-based proteomic analysis DNA testing mandatory	Biopsy of affected organs, immunohistochemistry of amyloid deposits or mass-spectroscopy-based proteomic analysis DNA testing mandatory	Typical eye and skin manifestations DNA testing
Genetics	Val30Met almost the only mutation in Portugal and Sweden: accounts for 50% of mutations worldwide	16 mutations in *APOA1* gene Neuropathic pattern of symptoms associated with Gly26Arg mutation	Single-base mutation at nucleotide 654A in the gelsolin gene on chromosome 9 in Finland
Treatment	Liver transplantation or tafamidis meglumine Treatment of symptoms	Organ transplantation	Plastic surgery

Table: **Characteristics of familial amyloid polyneuropathies (FAPs)**

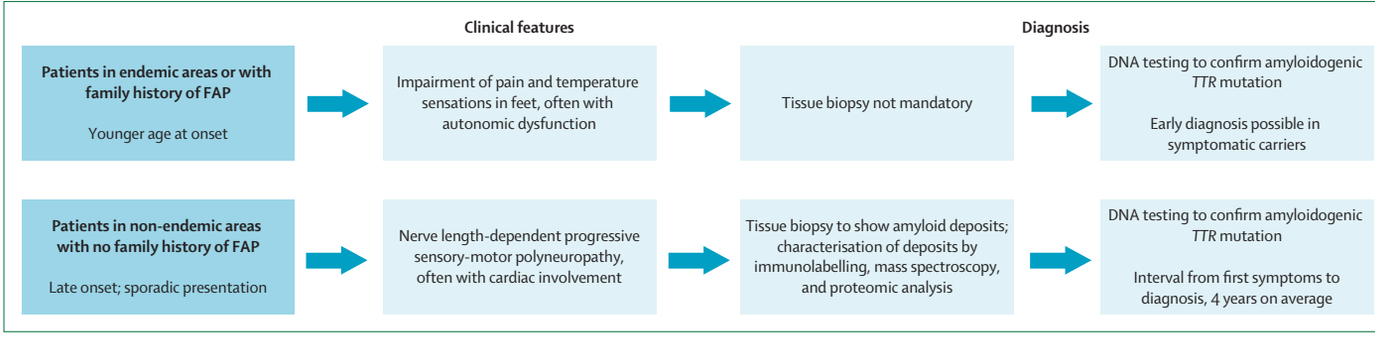

Figure 1: **Clinical presentation and diagnosis of early-onset and late-onset transthyretin familial amyloid polyneuropathy**
The symptomatology and clinical course of transthyretin (TTR) familial amyloid polyneuropathy (FAP) can be highly variable. Typical features of FAP in patients with early-onset and late-onset patterns of TTR amyloidosis are shown, with steps required to confirm the diagnosis.

involvement of light touch distally but with dissociated sensory loss still present proximally. The neurological deficit progresses relentlessly, with extension of sensory loss up the legs. Motor deficit occurs in the feet and lower legs, along with impairment of light touch and deep sensations, in relation to the involvement of larger sensory and motor nerve fibres. Walking becomes increasingly difficult, with loss of balance and stepping gait. Neuropathic pain is often of the burning type, is worse at night, and is associated with allodynia. However, pain is not a symptom in all patients. During the following months and years, the sensory deficit gradually extends to the thighs and then to the upper limbs. The fingers and gradually the forearms are affected as the anterior trunk becomes involved. The motor deficit also follows a length-dependent progression, and walking without an aid becomes increasingly difficult. Life-threatening autonomic dysfunction is present at this stage along with weight loss and muscle wasting. Loss of pain sensation with preservation of normal or subnormal strength can cause patients to experience painless trauma and development of plantar ulcers and foot osteoarthropathy (Charcot joints). However, in some patients, light touch is also affected early, but proprioception is spared in most cases.

Early-onset vs late-onset FAP

Late-onset FAP was identified decades after the early-onset pattern. Differences exist in the presentation of early-onset cases in endemic areas and late-onset cases in non-endemic areas (figure 1). In a series of patients aged over 50 years who had the TTR Val30Met mutation and who were from outside the endemic areas in Japan, there was a 10:1 preponderance of males to females. The most common initial symptom was paraesthesias in the legs, with mild symptoms of autonomic dysfunction, frequent cardiac involvement, low penetrance, and a family history in only one-third of patients.[10,11]