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# Transthyretin-related Familial Amyloid Polyneuropathy: A Case Report

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**Abstract**

**BACKGROUND:** Hereditary amyloidosis transthyretin is an autosomal dominant disease caused by heterozygous mutations in the transthyretin gene. The disease is characterized by amyloid deposits in various organs, primarily in the peripheral nerves and the myocardium.

**CASE PRESENTATION:** A 53-year-old female patient with the onset of symptoms 2 years earlier, presented with fatigue, difficulty walking, progressive muscle weakness, tingling in the hands and feet, blood pressure variations, weight loss, and constipation. There was no positive family history of familial amyloid polyneuropathy (FAP). Electromyography revealed sensorimotor axonal neuropathy; electrophoresis of cerebrospinal fluid was of transudative type, without immune activity in the central nervous system, while echocardiography detects hypertrophic myocardium and interventricular septum.

**CONCLUSION:** All patients who show symptoms of peripheral neuropathy with predominant signs of autonomic nervous system damage and hypertrophic cardiomyopathy should be referred for genetic testing for FAP.

## Introduction

Familial amyloid polyneuropathies (FAPs) are a group of life-threatening multisystem disorders transmitted as an autosomal dominant trait [1]. Hereditary transthyretin familial amyloid polyneuropathy (TTR-FAP) is a rare, but severe form of hereditary peripheral neuropathy in adults. It is the most disabling hereditary neuropathy affecting sensory, motor, and autonomic nerves, and is irreversible and fatal within 7–12 years of onset in the absence of therapy [2].

TTR is a secreted polypeptide chain consisting of 127 amino acid residues with an approximate mass of 14 kDa and a prominent β-sheet secondary structure. Mutations in the TTR gene, located on the 18th chromosome, can be associated with hereditary forms of amyloidosis transthyretin (ATTR) that are transmitted as an autosomal-dominant trait [3].

The amyloid accumulation in the peripheral nerves causes distal symmetrical polyneuropathy with neuropathic pain and sensory loss, autonomic dysfunction (e.g., fainting, gastrointestinal symptoms), and motor impairment [4].

As of today, reports of about 100 different points of single or double mutations or of a deletion in the TTR gene have appeared; most of these cases involve small kindreds or no family history [5].

## Case Presentation

We present a 53-year-old female patient with fatigue, difficulty walking, progressive muscle weakness, and tingling in the hands and feet. The first signs appeared 2 years ago, and since then the symptomatology continued to develop gradually. Significant worsening of the symptoms is noted 1 year ago following a serious case of virosis when the tingling feeling in the fingers of both feet and hands gradually spread to the elbows and the middle of both upper legs. The findings are followed with blood pressure variations, constipation, and continuous weight loss (15 kg in 2 years).

The previous medical records reveal a diagnosed hypertrophic cardiomyopathy, two ectopic pregnancies, and splenectomy, and from the family history, we note a

father diagnosed with Parkinson's disease and a mother deceased due to colorectal carcinoma. It is important to emphasize that this patient has no family history of FAP.

During the neurological examination, we note a generalized reduced gross motor strength, predominantly of the proximal musculature of the lower limbs, with the presence of hypotrophy of the muscles above and below the knee. The Gowers sign (a sign that presents with any condition that is associated with weakness of the pelvic girdle or proximal muscles of lower extremities [6]) was positive, with present peripheral paresthesia, paraparetic walking, not possible on heel and toes. Furthermore, vegetative symptomatology with gastroparesis, disturbed gastrointestinal tract motility, and blood pressure variations were also present.

The routine biochemical tests (complete blood count, glycemia, degradation products, electrolyte status, enzyme, and lipid status) showed no abnormal findings. The urine was cloudy, with leukocytes present in sediment, negative for nitrites. The thyroid hormones and tumor markers (AFP, CEA, Ca 15-3, Ca 19-9, Ca 125, and HCG) were also within reference ranges. We conducted a protein electrophoresis of cerebrospinal fluid which was of transudative type, without immune activity in the central nervous system.

Electromyography examination shows spontaneous denervation activity of the type of fibrillation potentials in m. genioglossus, m. tibialis anterior dexter, m. quadriceps femoris sinister, m. gastrocnemius sinister, and fasciculations in m. abductor digiti minimi dexter and m. gastrocnemius sinister. The electroneurography examination of the motor nerves registered prolonged latencies with slightly to moderately decreased motor conduction velocities for n. peroneus profundus bilaterally and n. tibialis bill (Table 1). The elecrtoneurography investigation of the sensory nerves registered unmeasurable sensory conduction velocities (SCV) for n. surrealism bilaterally and prolonged latency with reduced SCV for n. medianus sinister (Table 2).

**Table 1: Prolonged latencies and decreased MCV for n. peroneus profundus bilaterally and n. tibialis bilaterally**

| R/L | Nerve | Latency (ms) | MCV |
|---|---|---|---|
| L | n. medianus | 4.8 | 55.0 |
| L | n. ulnaris | 2.8 | 50.0 |
| L | n. peroneus profundus | 4.4 | 32.6 |
| R | n. peroneus profundus | 4.0 | 38.0 |
| R | n. tibialis | 5.6 | 36.0 |
| L | n. tibialis | 7.2 | 35.3 |

MCV: Motor conduction velocities.

Particularly important is the results from the conducted imaging examinations. The echocardiographic examination showed concentric hypertrophy of the left ventricle (LV) myocardium with no visible outbursts in myocardial kinetics, good systolic function, and EF%: 70%. Interventricular septum significantly hypertrophied, altered with nodular substrates present in the tissue. The SPECT scan of the myocardium with 99mTc-PYP showed intense and diffuse pathological cardiac accumulation of the radiotracer in the LV, a finding indicative of cardiac amyloidosis.

**Table 2: Prolonged latency with reduced SCV for n. medianus sinister. n. surrealism registered unmeasurable SCV**

| R/L | Nerve | Latency (ms) | SCV |
|---|---|---|---|
| L | n. medianus | 3.9 | 41.0 |
| L | n. ulnaris | 2.4 | 58.3 |
| R | n. surplus | | Unmeasurable |

SCV: Sensory conduction velocities.

Furthermore, the patient was sent to Macedonian Academy for Sciences and Arts (MANU) for a genetic testing where a pathogenic variant 325G>C (Glu109Gln) was detected, after which the final diagnosis of TTR-related FAP was made.

The patient started therapy with tafamidis 61 mg daily, duloxetin 60 mg once a day every morning, and pregabalin 75 mg daily. Duloxetin and pregabalin were implemented for neuropathic pain relief. The advice of a cardiologist: The patient continued her regular therapy with Aspirin 100 mg, Losartan 50 mg, and Presolol 50 mg daily. A recommendation for physical and rehabilitation treatment was also given.

## Discussion

Hereditary amyloidosis TTR-related is a rare disease associated with several point mutations in the TTR gene, determining abnormal aggregations of the TTR protein in different organs [7]. The natural course of TTR-FAP can be classified into three Stages: I (sensory polyneuropathy), II (progressive walking disability), and III (wheelchair-bound or bedridden) [8], with a life expectancy ranging from 7 to 12 years from onset.

As a rare disease, the European prevalence of amyloidosis (including secondary amyloidosis) was estimated at 47/100,000 in 2014 [9]. The most common TTR mutations worldwide are Val30Met, Val122Ile, and Glu89Gln [10]. An endemic cluster of cases has been occurring in Macedonia in recent decades. All patients and carriers are from the region of eastern Macedonia. Dominant cases are Delchevo, Berovo, Vinica, and Strumica. The most common pathogenic mutation in the TTP gene registered is Glu109Gln.

Since it is an autosomal dominant hereditary mutation in the TTR gene, the family history and the screening is extremely important in families with FAP. Genetic testing and counseling for the families are available today for the family members of patients with FAP at the MANU.

TTR-FAP is a highly heterogeneous disease and for its early diagnosis it is important to pay attention to the so-called red flag symptoms: 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,

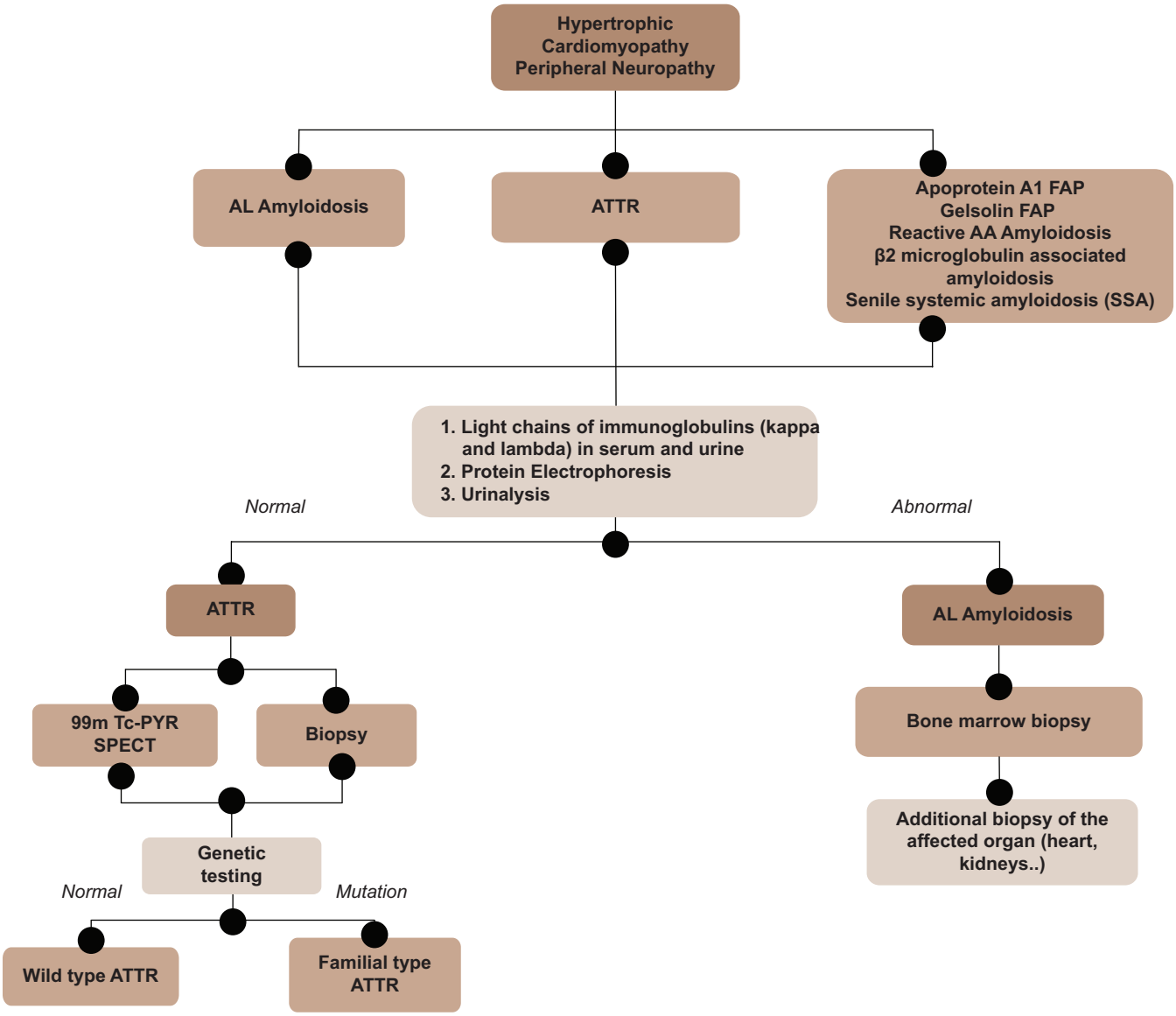


*Figure 1: Diagnostic pathway of ATTR and possible differential diagnoses. Mainly we differentiate ATTR from AL Amyloidosis by analyzing the presence of light chains of immunoglobulins in serum and urine, protein electrophoresis and analyzing urine for proteinuria*

carpal tunnel syndrome, renal impairment (albuminuria), or ocular involvement (vitreous opacities) [11].

In a patient with hypertrophic cardiomyopathy and peripheral neuropathy, we can think of several types of amyloidosis: Systemic amyloidosis, ATTR type amyloidosis (which can occur as wild type or hereditary form) and some of the other rare forms including: Apoprotein A1 FAP, Gelsolin FAP, Reactive AA amyloidosis, β2 microglobulin associated amyloidosis, and senile systemic amyloidosis (Figure 1).

For further differentiation, we approach the analysis of the presence of (1) light chains of immunoglobulins (kappa and lambda) in serum and urine; (2) protein electrophoresis; and (3) urinalysis for proteinuria.

If we get a normal finding, as in our case, then we raise a suspicion of ATTR, which we confirm with 99m Tc-PYR SPECT and a biopsy of the gingiva, gastric, rectal mucosa, fatty tissue or biopsy of the nerve-n surplus with Congo red staining and finally with Genetic testing of the gene for TTR on chromosome 18 for existing mutations, which is performed at MANU.

On the other hand, if we note light chains of immunoglobulins (kappa and lambda) in serum and urine, positive protein electrophoresis, and proteinuria, we continue the investigations in the direction of systemic type amyloidosis with a bone marrow biopsy and consultation with hematology.

The treatment options for TTR-related FAP are limited. Liver transplantation that replaces the variant TTR by the donor wild-type TTR was the first proposed treatment as a procedure that improves survival, especially in patients under 50 years of age with the Val30Met variant [12]. However, liver transplantation rarely improves nerve function, has no effects on manifestations such as eye lesions or cardiac involvement, is limited by the availability of a donor's liver, and requires lifetime immunosuppressant therapy,

which may in turn result in adverse clinical outcomes (e.g. increased risk of infections) [13]. Today, the most promising treatment option for patients is implementing an oral TTR stabilizer (tafamidis) which should be started as soon as the diagnosis is established.

Tafamidis is a first-in-class therapy that slows the progression of TTR amyloidogenesis by stabilizing the mutant TTR tetramer, thereby preventing its dissociation into monomers and amyloidogenic and toxic intermediates [14]. However, even though the drug slows down, it does not prevent the progression of the disease. A 10-year clinical study conducted by Merlini *et al*. [15] evaluated the effects of tafamidis on mortality in Val30Met and non-Val30Met patients with ATTR-PN. During the 10-year extension study, patients once a day orally administrate 20 mg tafamidis meglumine. Tafamidis has been shown to delay neurological disease progression in ATTR-PN and more recently to reduce the risk of mortality in TTR amyloidosis with cardiomyopathy. Furthermore, the median duration from disease onset to death reported in the literature is ~ 10 years (although this can vary considerably based on genotype and phenotype), whereas in the present study, 75–85% of patients treated with tafamidis are still alive ~ 8–9 years after starting tafamidis treatment, which is estimated as ~ 11–14 years after disease onset [15].

Some of the other promising treatments include Patisiran and Inotersen, RNA inhibitors which prevent the synthesis of TTR and by reducing the concentration of circulating TTR slow down the progression of neuropathy [16]. There are still ongoing clinical trials for implementing human monoclonal antibodies in the treatment of ATTR polyneuropathy. Antibody binding mediates the elimination of ATTR aggregates through phagocytes, which potentially leads to amyloid clearance [17]. Two drugs in this category have reached the clinical development pipeline, both designed to inhibit fibril formation through specifically targeting misfolded TTR, namely PRX004 and NI006 [18].

## Conclusion

Identification of ATTR amyloid polyneuropathy can be challenging, especially in non-endemic regions. Patients may present with heterogeneous symptoms often leading to a misdiagnosis of diabetic neuropathy or chronic inflammatory demyelinating polyradiculoneuropathy. Thus, all patients who have symptoms of peripheral neuropathy with predominant signs of autonomic nervous system damage and hypertrophic cardiomyopathy should be referred for genetic testing for FAP. A timely and accurate diagnosis of ATTR amyloidosis allows for early treatment and potentially modifies disease progression in patients.

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