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Single-centre experience on transthyretin familial amyloid polyneuropathy: case series and literature review

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Single-centre experience on transthyretin familial amyloid polyneuropathy: case series and literature review

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Abstract

Familial amyloid polyneuropathy (FAP) is a most often length-dependent axonal neuropathy, often part of a multisystem disorder also affecting other organs, such as cardiac, gastrointestinal, genitourinary, renal, meningeal and eye tissue. It is most frequently the result of a mutation in the TTR gene, most commonly a p.Val50Met mutation. TTR-FAP is a rare autosomal dominant heritable disabling, heterogeneous disease in which early diagnosis is of pivotal importance when attempting treatment. This paper discusses the course of four Belgian FAP patients with different TTR mutations (p.Val48Met; p.Val52Ala; p.Ala59Val; p.Val50Met). We also review the diagnosis and differential diagnosis of TTR-FAP, diagnostic studies, follow-up, its current treatment and those in development, prognosis and the importance of genetic counselling. At first TTR-FAP is often misdiagnosed as a chronic inflammatory demyelinating polyneuropathy or chronic idiopathic axonal polyneuropathy. Genetic testing is obligatory to confirm the diagnosis of TTR-FAP, except in familial cases. Biopsy samples are an asset in diagnosing TTR-FAP but can be falsely negative. At the moment, tafamidis meglumine is considered as first-line treatment in stage I neurological disease. Patients eligible for liver transplantation should be carefully selected when first-line therapy fails.

Key words: transthyretin familial amyloid polyneuropathy; liver transplantation; tafamidis meglumine; genetic testing.

Introduction

Familial amyloid polyneuropathies (FAPs) are a group of acquired or hereditary, autosomal dominant disorders that affect several organs. Three main types are distinguished, dependent on the precursor protein of amyloid: transthyretin (TTR), being the most prevalent type, gelsolin and apolipoprotein A-1. TTR, a homotetrameric protein, is mainly produced in the liver, whereas a small amount is produced by the choroid plexus and retinal cells. Pathogenic mutations induce the dissociation of the tetramer. Subsequent extracellular release of the monomers causes them to self-aggregate and ultimately create insoluble amyloid fibrils which precipitate in multiple tissues. The most frequent mutation is the p.Val50Met mutation, formerly known as Val30Met [1,2].

Clinical presentation

The main clinical feature of TTR-FAP is a length-dependent sensorimotor polyneuropathy which often precedes marked autonomic dysfunction. The polyneuropathy starts in the feet with loss of temperature and pain sensation, or neuropathic pain. It extends progressively above the ankles with involvement of light touch distally but dissociated sensory loss proximally. Motor deficits also start in the feet and follow a length-dependent pattern. The sensory deficit progresses to the fingers, forearms and eventually the trunk. There are three stages of TTR-FAP. In stage I, the disease is limited to the lower limbs with slight weakness of the extensor hallucis muscles. In stage II, the hand muscles become wasted and weak. In stage III, the patient is bedridden or confined to a wheelchair [3]. Less frequently the pattern is not length-dependent but focal, resulting from amyloid deposits. Carpal tunnel syndrome, for example, results from endoneurial amyloid deposition in the median nerve. Autonomic dysfunction is often prominent and mostly impairs cardio-circulatory, genitourinary and gastrointestinal systems leading to cardiac conduction failure, orthostatic hypotension, erectile dysfunction, cachexia, gastroparesis, postprandial diarrhoea or constipation. Eye involvement manifestations include vitreous opacities with progressive visual loss, chronic open-angle glaucoma due to trabecular obstruction, and scalloped pupils. Progressive renal failure may occur [1]. Familial amyloid cardiomyopathy (FAC) occurs when the mutated TTR precipitates in cardiac tissue. FAC should be distinguished from age-related or senile systemic amyloidosis in which misaggregation and subsequent precipitation of wild-type TTR leads to wild-type TTR-related amyloid cardiomyopathy. This heart disease is slowly progressive and clinically well tolerated until marked conduction disease, ventricular wall thickening and profound diastolic dysfunction occur [4].

Age of onset for early-onset FAP varies between the third to fourth decade. For late-onset FAP, it may vary between the sixth and eighth decade. It is endemic in Portugal, Sweden and Japan and shows a merely sporadic

presentation worldwide. Death occurs within ten years on average [1,5]. Table 1 shows the main differences between early- and late-onset Val50Met TTR-FAP [3].

TTR-FAP is a clinically heterogeneous disorder. The factors which influence its phenotype remain unclear. In non-Val50Met mutations, for example, cardiomyopathy seems to be more common among men with a late onset compared to women with a late onset [1,6].

Auxiliary investigations

Electromyography

EMG may initially be normal in cases of small-fibre polyneuropathy. In an advanced stage of the disease, large fibres are also affected, showing a length-dependent axonal sensorimotor polyneuropathy. Demyelinating features are less common but may lead to confusion with chronic inflammatory demyelinating polyneuropathy [3].

Cerebrospinal Fluid

Although usually normal, CSF protein content may be raised in TTR-FAP. TTR itself is predominantly produced in the liver but production in the choroid plexus also occurs. This results in the presence of TTR protein in CSF, sometimes leading to meningeal amyloid deposition [1,7].

Histology

Biopsy samples can be taken from (sural) nerve tissue, heart, muscle, kidney, gastrointestinal tract, the labial salivary gland and, most commonly, subcutaneous abdominal fat [3,4]. Extracellular amyloid deposits are visualized using Congo red staining. The amyloid deposits display a characteristic apple-green birefringence under polarised light examination. Additional immunohistochemical stains to identify amyloid protein components are mandatory. A negative biopsy, however, does not rule out amyloidosis [1,6,8]. Although the amyloid nature can be demonstrated with staining, the amyloid sub-type has to be proven using mass-spectroscopy-based proteomic analysis or immunohistochemistry [1,5]. A high index of suspicion and an experienced pathologist are needed for a correct diagnosis.

Neural amyloid deposits are mostly found in the endoneurium and endoneurial capillaries in an asymmetric manner between and in the fascicles. The destruction of unmyelinated fibres may be visualised early on electron microscopy, as well as vanishing of the Schwann cell basal lamina following contact with the amyloid deposits, rendering unmyelinated vessels dystrophic [1].

MR Neurography (MRN)

A recent study has provided class III evidence that MRN accurately identifies asymptomatic mutated TTR carriers [9].

Genetic testing

The *TTR* gene is located on chromosome 18q11.2-12. It contains four exons. One hundred nineteen mutations in the *TTR* gene have been reported, all of which are missense point mutations except for one microdeletion. One hundred thirteen mutations are amyloidogenic. The p.Val50Met point mutation is by far the most frequent mutation in endemic areas. DNA testing is mandatory for the diagnosis, except when typical symptoms manifest in cases with a known family history of TTR-FAP [1].

Own cases

We report four cases of TTR-FAP. Three have rare non-Val50Met *TTR* mutations. Table 2 shows a summary of the main features of these four patients.

Case one concerns a male with a p.Val48Met *TTR* mutation who deceased at the age of 64 years. This patient was initially diagnosed as chronic inflammatory demyelinating polyneuropathy (CIDP) in 1998 based on a sporadic chronic sensorimotor polyneuropathy with areflexia, combined axonal and demyelinating features on EMG, and a markedly elevated protein content in CSF. Several treatment attempts (plasmapheresis, administration of IV immunoglobulins, oral methylprednisolone, oral cyclophosphamide and the anti-CD20-monoclonal antibody rituximab) were of no avail. Early in his disease course, a sural nerve biopsy had been read as mixed axonal and demyelinating, with reportedly negative findings after Congo red staining. Multiple autonomic denervation symptoms developed and dramatically evolved along with marked weight loss. In January 2012 no amyloidosis was withheld on a rectal and abdominal fat tissue biopsy. Cardiac and ocular amyloidosis involvement were excluded. Genetic testing revealed a p.Val48Met (c.142G>A) *TTR* mutation which led to the final diagnosis of TTR-FAP. By the time of the correct diagnosis, the patient was confined to a wheelchair, suffered from extreme muscle wasting and severe autonomic symptoms such as severe orthostatic hypotension, erectile dysfunction and intestinal motility disorders with profound cachexia. He also suffered from a secondary depression. No etiological treatment could be given, resulting in death due to severe autonomic failure in 2012.

Case two concerns a male with a p.Val52Ala *TTR* mutation who deceased at the age of 44 years. Symptoms started at the age of 40 years with distal leg neuropathic pain, cachexia, gastrointestinal dysmotility, erectile dysfunction and an axonal sensory more than motor neuropathy on EMG, raising suspicion of TTR-FAP. Prompt genetic testing confirmed the diagnosis later that year revealing a p.Val52Ala (c.155T>C) *TTR* mutation. Family history was negative. Extensive cardiac evaluation was normal. Tafamidis was administered, and the patient was stable until orthotopic liver transplantation was performed eleven months later. Several bile duct strictures occurred during follow-up, resulting in multiple hospitalizations. Although liver transplantation was judged as successful, autonomic denervation progressed rapidly with severe orthostatic hypotension, cachexia and anorexia. Tafamidis was no longer accepted for reimbursement post-liver transplantation. Diflunisal was used without apparent benefit for 8 months prior to his sudden death in 2016.

Case three is a 43-year-old male with a p.Ala59Val *TTR* mutation. Symptom onset occurred in 2014. Initial complaints at age 41 included distal lower limb neuropathic pain, gastrointestinal dysmotility, erectile dysfunction, unexplained orthostatic syncope and rapid weight loss. A cardiac hypertrophy of unknown cause was observed two years earlier. EMG showed a mild length-dependent distal lower limb symmetric sensorimotor axonal neuropathy. Diagnosis of TTR-FAP was based on prompt genetic testing which showed the p.Ala59Val (c.176A>T) *TTR* mutation. His father and paternal uncle had deceased due to a cardiac disorder of unknown etiology. Genetic analysis of his asymptomatic paternal cousin showed the same mutation. Cardiac evaluation demonstrated left ventricular hypertrophy with on the ECG a QS-pattern in the anterior leads – compatible with a pseudo-infarct appearance as the anterior segments were still contractile – suggesting an infiltrative cardiomyopathy. Endomyocardial biopsy confirmed TTR-immunoreactive amyloid deposition. In June 2016, a pacemaker was implanted following a severe syncope and documentation of a high grade AV-block. Tafamidis therapy started in 2015 and is continued. The patient was initially stable, then had improved general and neurologic condition with weight gain and improved exercise capability. After 2 years, orthostatic hypotension remains the main symptomatic problem. Cardiac function is stable. Combined heart and liver transplantation was considered but withheld as the clinical condition was generally improved.

Case four concerns a 72-year-old male with a p.val50Met *TTR* mutation. Symptom onset occurred at the age of 70 years with neuropathic pain and autonomic denervation signs in the feet, and intrinsic foot muscle atrophy and weakness, mild bilateral foot drop, sensory ataxia and lower limb areflexia. EMG showed a severe length-

dependent distal symmetric sensorimotor axonal neuropathy. Until genetic testing confirmed TTR-FAP diagnosis, the patient was diagnosed with chronic idiopathic axonal polyneuropathy. No evidence for cardiac impairment was withheld. Two of his children show the same mutation after DNA testing, one of which experiences a minimal sensory neuropathy. The patient is currently stable under treatment with tafamidis, symptomatic neuropathic pain treatment and physiotherapy. He refuses liver transplantation but is not eligible anyway according to current liver transplantation criteria.

Discussion

Diagnosis and differential diagnosis

In the presence of a positive family history, sensorimotor and autonomic polyneuropathy should raise suspicion of TTR-FAP. In the absence of a positive family history, a length-dependent axonal polyneuropathy predominantly affecting pain and temperature sensation may indicate TTR-FAP, especially when combined with cardiac involvement, prominent autonomic denervation signs and cachexia [1,5]. There is an average of one to four years between the onset of first symptoms and diagnosis [1,5]. To confirm amyloidosis, amyloid deposition has to be demonstrated on biopsied tissues and DNA testing should be performed [1,5]. Another possible cause of amyloidosis is light-chain amyloidosis because of its high incidence in the elderly population. Assessment for serum and urinary free lambda and kappa light chains should be performed [3,4].

CIDP is the most frequent misdiagnosis. CSF protein content can be raised and nerve conduction velocity may be decreased in FAP, although axonal involvement is most common. The differential diagnosis includes the following disorders: idiopathic axonal polyneuropathy, lumbar spinal stenosis, diabetic polyneuropathy, chronic alcoholism, Charcot-Marie-Tooth neuropathy, motor neuron disease and paraneoplastic syndrome [1,6].

Therapy

Targeted therapy

Next to symptomatic therapy, targeted therapy should be started as soon as possible to prevent further production of amyloid deposits.

Tafamidis meglumine

Tafamidis stabilizes the mutant TTR tetramer by binding to the thyroxine binding sites, preventing its dissociation into monomers. For the treatment of TTR-FAP in adult patients with stage I symptomatic polyneuropathy, it is currently in clinical use in Europe in a single daily oral dose of 20 mg. Its efficacy has been

proven in both Val50Met and non-Val50Met TTR mutations. It is well tolerated and increases the quality of life. Its long-term efficacy is currently being assessed [1,3,6,10].

Diflunisal

Diflunisal, a nonsteroidal anti-inflammatory drug, is currently not licensed for the treatment of stage I and stage II TTR-FAP. It prevents the dissociation, misfolding and misassembly of the mutated TTR tetramer. A single multicentre study of Berk *et al.* has shown that diflunisal inhibits polyneuropathy progression and increases quality of life in TTR-FAP patients with various stages of disease. Gastrointestinal, cardiac and renal side effects may make its use problematic. Further investigations concerning its safety and effect will have to determine its potential use [6,11].

Liver transplantation

Liver transplantation stops the production of the mutated TTR in the liver but not in the choroid plexus and retinal epithelium. Ocular, leptomeningeal and cerebral manifestations such as TIA-like episodes, stroke, aura-like episodes and epileptic seizures are thus not influenced by liver transplantation [1,3,5,12,13]. Survival-rate post-liver transplantation is worse in non-Val50Met TTR-FAP: the five-year survival rate for non-Val50MetTTR-FAP is 50-60% compared to 80-82% in Val50Met TTR-FAP [1,3,6,14].

It has been reported that a longer preoperative disease course of FAP is a negative prognostic factor for liver transplantation. It should therefore be performed rather early than late. However, recent guidelines suggest to continue tafamidis therapy as first-line therapy, and keep liver transplantation in reserve until clinical progression under tafamidis occurs [1,5,6,15]. Side effects of transplantation and reports of negative neurological evolution despite liver transplant, as in our second patient, were also considered when formulating this guideline [16].

Contraindications for liver transplantation include: active and uncontrolled cancer; age >50 years for males and >70 years for females; modified body mass index below 800 kg g/L m²; some non-Val50Met TTR mutations; cardiac insufficiency. However, a combined heart and liver transplantation may be considered in selected cases [6]. Some mutations are known to frequently cause cardiac or combined cardiac and neurological involvement. The mutation in our third patient is very rare and causes combined cardiac and neuropathic disease. One other published case had combined involvement as well [17] .

In case of domino liver transplantation, where a patient with a severe liver disease receives a liver from a FAP patient, the domino liver transplantation acceptor is at risk of developing FAP. Except for the production of mutated TTR, a normal liver function is required to qualify for domino transplantation. In half of the patients,

amyloid deposits were observed in labial salivary glands five years after domino liver transplantation. Nonetheless, it is still done because of the shortage of donor livers [3].

Therapies in development

New therapies that are currently being developed include posttranscriptional gene silencing (using small interfering RNA (siRNA) or antisense oligonucleotides), immunotherapy using antibodies and a combination of doxycycline-tauroursodeoxycholic acid [3,6].

The use of siRNA was shown to interfere with gene expression through RNA interference. Substantial and prolonged down-regulation of TTR protein level was observed following treatment with the siRNA ALN-TTR01 and ALN-TTR02. The phase 3 APOLLO study with Patisiran (ALN-TTR02) that has recently been completed shows promising results concerning polyneuropathy symptoms, quality of life, exploratory cardiac measures, safety and tolerability (D. Adams, personal communication). Another phase 3 study involving ISIS 420915, an antisense oligonucleotide, is in its final stage [18]. Postponing liver transplantation until results of these studies are known should be considered [6]. Studies on clinical efficacy and safety of long-term TTR knockdown have not been performed yet. The decrease in retinol-binding protein levels due to TTR knockdown is a possible adverse effect. An advantage compared to liver transplantation is that the siRNA ALN-TTR02 knocks down both the mutant and wild-type TTR [18].

Current treatment guidelines

Tafamidis is used as first-line therapy in stage I FAP. Eligibility for liver transplantation should be checked in case of progression of the disease. Off-label use of diflunisal or inclusion in clinical trials should be considered in stage II FAP. Figure 1 shows a treatment algorithm for TTR-FAP, developed by the European Network for TTR-FAP (ATTReuNET) [6].

Follow-up and prognosis

Neurological, cardiac, renal and ocular examination should be done periodically in all TTR-FAP mutation carriers, whether symptomatic or asymptomatic. Neurological examination consists of sensory, motor and reflex evaluation, EMG, assessment of postural blood pressure and heart rate variability, and the presence of carpal tunnel syndrome. Cardiac screening involves performing an electrocardiogram and echocardiogram, and measurement of BNP or NT pro-BNP. Detection of clinical manifestations in TTR-FAP carriers confirms the diagnosis and should result in therapy (Fig. 1). Symptomatic treatment and psychological support should also take place [1,8].

Death resulting from progressive cardiac amyloidosis has also been reported post-liver transplantation. This is most probably due to cardiac wild-type TTR deposition. Thus, when considering liver transplantation, assessment of cardiac function and post-transplantation follow-up is of utmost importance. Following liver transplantation, patients with an early onset, Val50Met mutation and shortened duration of the disease have a better prognosis than patients with late onset, non-Val50Met mutation and prolonged duration of the disease [6]. Due to the local mutated TTR synthesis in the choroid plexus and retinal epithelium, the ocular and nervous system may deteriorate despite liver transplantation, resulting in, among others, chronic open-angle glaucoma and cerebral amyloid angiopathy. A significant increase of atrial fibrillation, a predictor of cerebrovascular events such as transient ischemic attacks, ischemic stroke, intracerebral hemorrhage and subarachnoid hemorrhage was observed in Val50Met FAP patients post-liver transplantation. Increased overall survival post-liver transplantation enables TTR-FAP patients to develop intracerebral amyloid deposits which increases the risk of brain hemorrhage. Immunosuppressive treatment following transplantation may render the patient susceptible to infections [1,3,5,6,12,16].

Genetic counselling

There is an urgent need for genetic counselling for patients and at-risk relatives [6]. Genetic counselling brings along several stressors for the patient and his or her relatives [1].

As mentioned, making the diagnosis early may be of pivotal importance in patient outcome. However, genetic testing for TTR-FAP before the age of 18 should not be done since its practice holds no medical benefit. This may change in the future depending on the acquisition of new insights or therapies. Prenatal genetic testing and pre-implantation genetic diagnosis can be considered in some families [8,19] .

In case of a positive genetic test, the gene carrier should not receive presymptomatic treatment since at this time it is not an accepted indication. The gene carrier should, however, be monitored regularly. Suspicion of symptom-onset matching with TTR-FAP should result in treatment [8].

Conclusion

FAP is a heterogeneous disease with a variety of possible symptoms, depending on which tissue is affected. A multiplicity of mutations has been described, each with a diverse expression. It is a rare disorder with major influence on the daily life of patients. When possible, patients that cannot undergo liver transplantation or get tafamidis should be enrolled in clinical trials to test efficacy and safety of new treatment modalities. In an early stage, liver transplantation is a valid option when symptoms are progressive despite tafamidis therapy, although

it does not eliminate the production of wild-type TTR and TTR production from retinal cells and the choroid plexus. Liver transplantation and the associated immunosuppressive treatment itself holds several risks. Therefore, additional prospective clinical research is necessary to assess the course and outcome of these non-Val50Met TTR mutations, especially in non-endemic regions.

Table 1

Course and characteristics of early- and late-onset TTR-FAP.

	Early-onset Val50Met TTR-FAP	Late-onset Val50Met TTR-FAP
Age of onset	<50 years	>50 years
Country	Portugal, Japan, Brazil	Sweden, France, UK, Italy, Japan
Positive family history	94%	48%
Initial clinical presentation		
Peripheral neuropathy	57%	81%
Autonomic neuropathy	48%	10%
Mean delay for walking aid	>5.6 years	3 years
Cardiac	Progressive conduction disorders	Restrictive cardiomyopathy Heart failure
Median survival	11 years	7.3 years
Causes of death	Cachexia, infections	Heart failure Sudden death Cachexia or secondary infection

TTR-FAP transthyretin familial amyloid polyneuropathy. Modified from [3].

Table 2

Summary of cases of TTR-FAP.

	Case one	Case two	Case three	Case four
Sex	Male	Male	Male	Male
Year of birth	1948	1972	1974	1945
TTR mutation	p.Val48Met	p.Val52Ala	p.Ala59Val	p.Val50Met
Symptom onset	1998	2012	2014	2015
Symptoms	Sensorimotor and autonomic polyneuropathy Neuropathic pain Muscle wasting Impotence Hypotension Intestinal motility disturbance	Sensory more than motor polyneuropathy Neuropathic pain Cachexia Impotence Hypotension Intestinal motility disturbance	Symmetric sensorimotor polyneuropathy in lower limbs Neuropathic pain Impotence Weight loss Hypotension Intestinal motility disturbance	Sensorimotor and autonomic polyneuropathy Neuropathic pain
First diagnosis	Chronic inflammatory demyelinating polyneuropathy	TTR-FAP	TTR-FAP with cardiac amyloidosis	Chronic idiopathic axonal neuropathy
Targeted treatment	None	Tafamidis Liver transplantation in 2014 Diflunisal	Tafamidis	Tafamidis
Outcome	Deceased in 2012	Deceased in 2016	Doing well on tafamidis therapy	Stable on tafamidis therapy
Peculiar findings	Negative sural nerve, rectal and adipose biopsy for amyloidosis	Negative evolution after liver transplantation	Mild improvement on tafamidis	None

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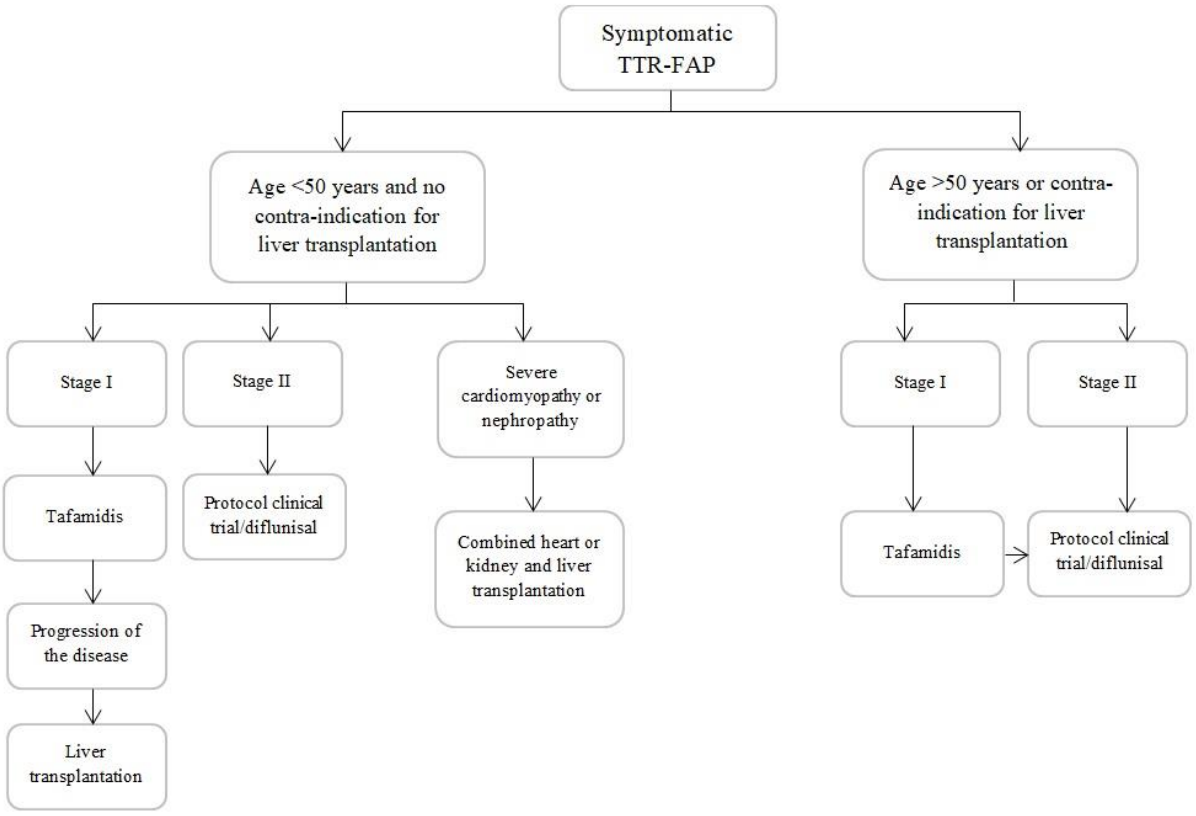
Fig.1 Treatment algorithm for TTR-FAP



Legend

Fig.1 Treatment algorithm for TTR-FAP

Stage I: walking unaided outside. Stage II: walking with aid. Protocol for clinical trials for antisense oligonucleotides, small interfering RNA, combination doxycycline-tauroursodeoxycholic acid; or diflunisal off-label. Modified from [6].

Compliance with Ethical Standards

Funding: The authors declare that no funding was involved.

Conflict of Interest: The authors declare that they have no conflict of interest.

Ethical approval: This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent: Informed consent was obtained from all individual participants included in the study.

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Symptoms	Sensorimotor and autonomic polyneuropathy Neuropathic pain Muscle wasting Impotence Hypotension Intestinal motility disturbance	Sensory more than motor polyneuropathy Neuropathic pain Cachexia Impotence Hypotension Intestinal motility disturbance	Symmetric sensorimotor polyneuropathy in lower limbs Neuropathic pain Impotence Weight loss Hypotension Intestinal motility disturbance	Sensorimotor and autonomic polyneuropathy Neuropathic pain
First diagnosis	Chronic inflammatory demyelinating polyneuropathy	TTR-FAP	TTR-FAP with cardiac amyloidosis	Chronic idiopathic axonal neuropathy
Targeted treatment	None	Tafamidis Liver transplantation in 2014 Diflunisal	Tafamidis	Tafamidis
Outcome	Deceased in 2012	Deceased in 2016	Doing well on tafamidis therapy	Stable on tafamidis therapy
Peculiar findings	Negative sural nerve, rectal and adipose biopsy for amyloidosis	Negative evolution after liver transplantation	Mild improvement on tafamidis	None

TTR-FAP transthyretin familial amyloid polyneuropathy.

Fig.1 Treatment algorithm for TTR-FAP

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