Amyloid neuropathies

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Purpose of review
As amyloid neuropathies have benefited from recent major progress, this review is timely and relevant.

Recent findings
The main recent articles on amyloid neuropathy cover its description, methods for diagnosis and therapies. Varied clinical presentations are described in transthyretin (TTR)-familial amyloidosis with polyneuropathy (FAP) and light chain amyloid neuropathy. Mass spectrometry is able to identify the biochemical nature of amyloidogenic protein in nerve biopsy and skin biopsy samples for diagnosis of small fiber polyneuropathy. Both nerve biopsy and *TTR* gene sequencing are important to identify sporadic cases of amyloid neuropathy. Nerve biopsy is useful in demonstrating the amyloid origin of neuropathies developing after domino liver transplant recipients. Liver transplantation improves long-term survival in Met30 TTR-FAP. Factors recognized as leading to cardiomyopathy progression or heart involvement after liver transplantation are late disease onset and fibril composition. Combined heart and liver transplantation is recommended in severe restrictive cardiomyopathy. Antiamyloid drugs are emerging: tafamidis, a TTR stabilizer, showed in a phase III controlled study its ability to slow stage 1 FAP progression. Other strategies are emerging for TTR-FAP (combination doxycycline–tauroursodeoxycholic acid, small interfering RNA, antisense oligonucleotide, monoclonal antibody antiserum amyloid P component). For light chain neuropathy, intensive chemotherapy may be helpful.

Summary
There is better recognition of amyloid neuropathies, and hope for enrolling patients with FAP in future clinical trials testing new antiamyloid drugs.

Keywords
AL, diagnosis, familial amyloidosis with polyneuropathy, therapy, transthyretin

INTRODUCTION

This review will focus on developments concerning amyloid neuropathies, including familial amyloidosis with autosomal-dominant transmission, essentially due to a point mutation of the transthyretin gene (*TTR*) and light chain (AL) amyloidosis [1]. Amyloid neuropathies are severe, progressive, disabling, irreversible and life-threatening diseases. Early diagnosis is crucial to propose antiamyloid treatment and slow or stop disease progression. In these neuropathies, diagnosis is still difficult; the scope of this review will include the spectrum of clinical presentations, clues and methods for diagnosis, and therapies, with special interest in innovative treatments.

TRANSTHYRETIN FAMILIAL AMYLOIDOSIS WITH POLYNEUROPATHY

TTR-familial amyloidosis with polyneuropathy (FAP) is the main cause of amyloid neuropathy.

Diagnosis

Endemic areas of TTR-FAP are Portugal [2], Japan, Sweden and Brazil. Diagnosis is easy because of a positive family history, high penetrance and a stereotypical clinical presentation as a length-dependent small fiber polyneuropathy (PNP) with autonomic dysfunction. Formal diagnosis requires *TTR* gene analysis showing Met30TTR mutation and positive labial salivary gland biopsy (LSGB) for amyloidosis [3].

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KEY POINTS

- The clinical spectrum of amyloid neuropathy has been considerably widened.
- The main tools for diagnosis are TTR gene analysis, LSGB or nerve biopsy.
- Early diagnosis of late onset amyloid neuropathy is important because its course is more severe.
- The therapeutic era opens with new antiamyloid medicines including tafamidis, the first drug approved for FAP by EMA.

In nonendemic areas, FAP is still underdiagnosed as amyloidosis is suspected in only in 26% [4▪] to 38% [5▪] of initial evaluations. Diagnosis of TTR-FAP is difficult and is delayed by 3 years [4▪,5▪,6▪▪] because of absence of positive family history (sporadic cases) in 52% [5▪] to 77% [4▪] and varied presentations. In late-onset patients (disease onset after 50 years), diagnosis is done at a stage of severe walking disability in 27–39% [5▪,7▪]. There are four phenotypes: small fiber PNP, length-dependent all fiber PNP, multifocal neuropathy in upper limbs and ataxic neuropathy [5▪].

FAP presents usually as a progressive cryptogenic axonal PNP in spite of a minimal screening [8]. Autonomic symptoms are inaugural in 10% of late-onset sporadic cases [4▪,6▪▪] and are never the chief complaint but will develop later in 47% [7▪] to 78% [5▪] of patients. Another frequent misleading diagnosis is chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) [4▪,7▪,9▪▪] due to diffuse areflexia, elevated cerebrospinal fluid (CSF) protein and some electromyography findings [4▪,7▪,9▪▪]. Absence of response to intravenous immunoglobulin (IVIg) should alert the physician [9▪▪]. More surprisingly, amyloid PNP may present with an upper limb neuropathy with numbness in the distal upper limb extremities at onset in 10% [6▪▪] to 23% of patients [5▪,7▪], misdiagnosed initially as a carpal tunnel syndrome [10]. Neuropathy may remain predominant and severe in upper limbs [10,11].

FAP may also mimic paraneoplastic, alcoholic neuropathy [7▪], Charcot–Marie–Tooth or hereditary neuropathy with liability to pressure palsy [4▪], systemic vasculitis, motor neuron disease [4▪,12▪] and lumbar spinal stenosis [5▪].

If TTR-FAP is a systemic disease, cardiac involvement is rarely symptomatic (7%) at the time of diagnosis [7▪], with heart failure in 14% of cases [6▪▪] and first-degree or second-degree atrioventricular blocks in 13% [6▪▪]. Cardiac involvement is found in 72% of cases when chest radiograph or echocardiography is performed [6▪▪].

One should evoke diagnosis of FAP in progressive and disabling PNP especially in the elderly [4▪,5▪,13], and propose nerve biopsy to reorient the diagnosis [7▪,9▪▪].

Natural history

The natural history of TTR-FAP was described 30 years ago in Portugal, with three stages: stage 1 with essentially sensory polyneuropathy; stage 2 with progressive walking disability leading to aid for walking; and stage 3 with wheelchair bound or bedridden patients, and lethal within 10.8 years after onset [2]. The sensory motor PNP in late-onset met30 TTR-FAP and Ser97 TTR-FAP has a faster evolution leading to early disability, use of a walking aid occurring within 3 years from onset, and some patients developing episodes of acute deterioration of weakness. Life expectancy ranges from 4.7 [13] to 7.3 years [6▪▪], most patients (71%) dying from cardiac disease [6▪▪].

Diagnostic methods

The investigations used for amyloid neuropathy are summarized in Table 1 [3,4▪,5▪,7▪,13,14▪,15,16▪▪,17▪]. Diagnosis usually requires detection of characteristic amyloid deposits after nerve biopsy, LSGB or abdominal fat aspiration (AFA). Sensitivity of nerve biopsy depends on the skills of the neuropathologist, and can be as high as 80% [4▪,5▪,7▪], reaching 93% after a second look of the biopsied specimen [7▪]. LSGB is used routinely in Portugal to detect amyloid deposits in symptomatic FAP patients with a sensitivity of 91%, but may be also positive in 18% of asymptomatic carriers [3]. AFA is poorly sensitive in 15% [4▪,17▪] to 83% [15] of cases. Immunohistochemistry is used to determine the biochemical nature of amyloid deposits but may not be not contributive. Use of laser microdissection and mass spectrometric-based proteomic analysis allowed detection of specific types of amyloid in all 21 cases evaluated, including acquired monoclonal immunoglobulin light chain (LC), gelsolin or TTR amyloidosis [16▪▪].

Skin biopsy can disclose severe intraepidermal nerve fiber density reduction in length-dependent PNP. Degeneration of cutaneous nerve terminals was correlated with the severity of clinical phenotypes and CSF protein level in the new mutation Ser97 TTR identified in Taiwan [13].

TTR-FAP exhibits a large genetic heterogeneity with many mutations (Table 2) [4▪,5▪,13,17▪,18,19,20▪] which have been progressively described in

Table 1. Investigations used in amyloid neuropathy

Investigation	Number of patients	Aim	Sensitivity	Specificity	Advantages	Inconveniences	Comment	References
Nerve biopsy	19	Detection of amyloid deposits	68%[a] amyloid neuropathy	High	Useful for differential diagnosis	Requires a good pathological laboratory	Gold standard in sporadic autonomic neuropathy	[14▪]
	15	Detection of amyloid deposits	80%[b] TTR	High		(Expertise)		[7▪]
	15	Detection of amyloid deposits	80% TTR	High	Useful for sporadic cases	Invasive		[4▪]
	27	Detection of amyloid deposits	80% TTR	High				[5▪]
Labial salivary gland biopsy	87	Detection of amyloid deposits	91% TTRMet30	High	Simple, repeatable	positive in asymptomatic patients (15%)		[3]
Proteomic analysis of nerve tissue, LMD/MS[a]	21	To determine specific type of amyloid deposits	Approximately 100%	High	Useful	Requires specialized laboratory Takes time	Only one laboratory in the world in routine	[16▪▪]
Abdominal fat aspiration	12	Detection of amyloid deposits	83%	High		Requires specialized laboratory		[15]
	14	Detection of amyloid deposits	14%, 33%[c]	high	Repeatable			[4▪,17▪]
Skin biopsy (punch)	19	Denervation; early marker of neuropathy	High	Low, other PNP	Repeatable	Needs specialized laboratory; not specific for amyloid neuropathy	Useful do detect early disease	[13]
TTR gene sequencing		Detection of TTR mutation gene carriers	100%	Very high		Nonamyloidogenic mutations Ser6, Thr119 Amyloidogenic mutations for leptomeningeal, cardiac, ocular amyloidosis		
EMG		Detection of axonal neuropathy	High	Low	Repeatable help for monitoring TTR mutation carriers	Not specific for amyloid neuropathy	Useful to follow patients after specific therapy	

LMD/MS, laser microdissection mass spectrometric-based proteomic analysis; PNP, polyneuropathy; TTR, transthyretin.
[a]increased to 79% after second look.
[b]increased to 93% after serial sections examination.
[c]increased to 50% after a second biopsy.

Table 2. Transthyretin mutations for familial amyloidosis with polyneuropathy worldwide

Country	Mutations (*n*)	% V30M	Mean age of onset (years)	Interval from onset to diagnosis (years)	% Late onset	Positive family story	Duration of the disease (years)	Reference
Portugal	2	99%	31.1		7%	98%	11	
Sweden	4	>95%	56.7	3.2	~75%	65%	NA	[18]
Japan	19	/	/	/	/	/	NA	[19]
	1	100% early	31.9	NA	0%	94%	>10	
	1	100% late	64.5	NA	100%	48%	7.3	[6▪▪]
France	29	66%	62	3.1	40% (89%[b])	60% (48%[b])	<10	[5▪]
Italy	8	35%	60.5	3.3	77%	23%	NA	[4▪]
	+1[a]	53%	66	4	100%	33%	NA	[17▪]
Taiwan	1	0%	59.5	NA	95%	0%	4.71[c]	[13]
UK	3	NA	63	2	~90%	37%	6.6	[20▪]

NA, not available.
[a]Three mutations previously reported in [4▪] including a new one.
[b]Excluding met30TTR-FAP patients of Portuguese origin.
[c]For 14 of 19 patients.

France (up to 29 TTR mutations) [5▪], in Japan [19], more recently in Italy [4▪,17▪], and also in Sweden, an endemic country for TTRMet30-FAP [18]. One can suppose that the genetic heterogeneity is worldwide, depending on the access to *TTR* gene analysis. The clinical presentation of the more common variant Ala60TTR in the UK is peripheral or autonomic dysfunction in 65% and cardiac involvement in the others [20▪]. It is a late onset and usually sporadic disease with a median survival of 6.7 years after onset [20▪].

Therapy

The aim of specific therapy of amyloid neuropathy is to prevent amyloidogenesis, and therefore limit the disease's progression. Until recently, it included liver transplantation for TTR-FAP and chemotherapy for AL amyloidosis.

TTR-FAP is associated with a high rate of conduction disorders and an increased risk of sudden death. Prophylactic pacemaker implantation prevents symptomatic bradycardia with high degree atrioventricular block [21▪].

Liver transplantation

For 20 years, liver transplantation has been proposed to remove the main source of mutant TTR. More than 2000 liver transplantations have been performed worldwide; 85% of patients had a Met30-TTR mutation [22▪].

In a prospective monocentric and long-term study of liver transplantation in 200 TTR-FAP cases, including 69% with Met30TTR and 37.5% with late onset, 20% of patients worsened and reached stage 2 (walking with a stick) during follow-up. Late onset, PND2 (on the Polyneuropathy Disability scale; indicates difficulties in walking but without need for a walking stick), and a weight loss more than 20% at liver transplantation were independent risk factors (Adams D, personal communication).

In a monocentric study with Met30TTR-FAP, the survival of 37 patients after liver transplantation was better at 10 years (100%) compared with the untreated group (56%) [23▪▪]. In the world liver transplantation-FAP register, the survival at 5 years is better in patients with the Met30TTR variant than other variants [22▪].

Cardiomyopathy may progress in FAP patients after liver transplantation. Late onset [24▪] and amyloid fibril composition of type A (a mixture of truncated and full-length TTR) [25▪] are the main predictors for increased interventricular wall thickness and for the development of cardiomyopathy. Progression has been shown in Ala60 TTR patients by NT-proBNP (amino-terminal fragment of pro-brain natriuretic peptide) concentration and interventricular wall thickness, with death after liver transplantation due from heart origin in three of eight patients [20▪]. Liver transplantation does not prevent the development of heart arrhythmia necessitating pacemaker implantation in Met30 TTR variant cases [26▪,27], nor ocular amyloid progression [28].

Progression of amyloid diseases after liver transplantation is mainly due to accumulation of wild-type TTR in patients. That was shown in the heart and more recently in the peripheral nervous system

in a patient who died after liver transplantation [29]; amyloid fibrils contained 75% wild-type TTR versus 40% in nontransplanted FAP patients [29]. Turnover of amyloid fibrils is more rapid in aging patients, and may play an important role in wild-type TTR-derived amyloid fibril formation in FAP patients [30▪] that is detected at higher proportion in late FAP patients [31▪].

Combined heart and liver transplantation (HLT) has been proposed in 10% of non-Met30TTR variant cases worldwide [22▪]. In a series of 20 patients with FAP who underwent liver transplantation, four underwent a HLT for restrictive cardiomyopathy [32]; four of 16 other patients (25%) died during the first year from cardiac cause [32].

Other therapies

(Fig. 1) Other therapies have been developed during recent years to offer alternative treatment for patients with contraindication to liver transplantation (age >70 years, active cancer and advanced-stage disease) or in late-onset FAP for which progression of the disease has been shown after liver transplantation.

Transthyretin kinetic stabilizers

TTR is a protein with a tetrameric conformation that is known to misfold, aggregate and undergo amyloidogenesis *in vivo*. Some TTR-FAP mutations destabilize the native quaternary and/or tertiary structure. TTR kinetic stabilizers (TKS) binding to the T_4 binding sites and stabilizing the TTR tetramer have been developed [33▪].

A multicentric phase II/III double-blind clinical trial (Fx-005), comparing placebo with tafamidis (20 mg/day), a TKS, enrolled 128 patients during 18 months. Criteria of primary judgment were the percentage of patients increasing no more than 2 points on the Neuropathy Impairment Score–Lower Limbs (NIS-LL) for neuropathy and the modification of the scale of total quality of life (TQOL). The average age of the met30TTR-FAP patients was 39 years, all with a mild neuropathy. A greater proportion of the patients in the group receiving tafamidis were NIS-LL responders than those in the group receiving placebo, with statistical significance in prespecified efficacy evaluable analysis of patients who completed. In this analysis, 60% of the patients in the tafamidis group were NIS-LL responders compared with 38% of the patients in the placebo group. The mean change from baseline in TQOL score in these patients was significantly lower in the tafamidis group than the placebo group [34▪]. Tafamidis is approved by European Medicines Agency (EMA) for use in the European Union. It is indicated for the treatment of TTR amyloidosis in adult patients with stage 1 (walking without aid) symptomatic

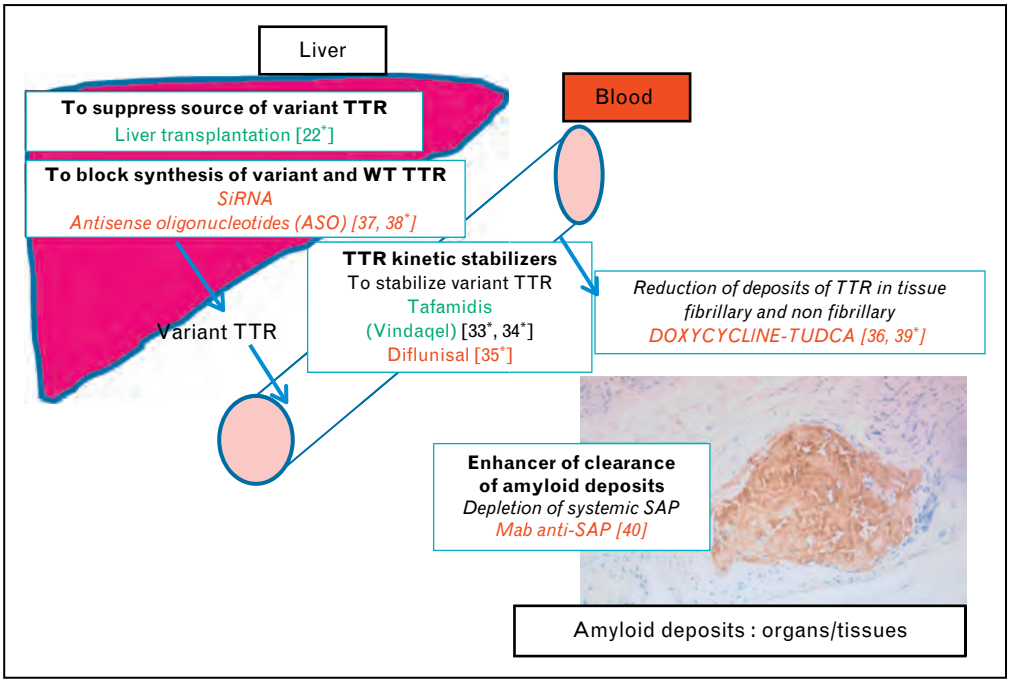

FIGURE 1. Therapeutical approaches in transthyretin familial amyloidosis with polyneuropathy. In green, therapy with proven clinical efficacy: C, tafamidis (Vyndaqel; Pfizer, New York, NY). In red, therapy with ongoing clinical trials with usually proven efficacy in experimental studies. Mab anti-SAP, monoclonal antibody anti-serum amyloid P component; TTR, transthyretin; TUDCA, tauroursodeoxycholic acid; WT, wild type.

polyneuropathy to delay peripheral neurologic impairment. Main adverse reactions are urinary tract infections, and diarrhea (≥ one of 10).

A recent phase I clinical trial showed that diflunisal kinetically stabilizes TTR tetramers in human plasma because of its excellent oral bioavailability and high plasma concentrations after oral dosing (250 mg, twice daily). A placebo-controlled multicenter phase III clinical trial is testing the efficacy of diflunisal for the treatment of FAP [35▪].

Other new therapies

The combination of doxycycline, which has properties of 'TTR fibrils breaker' *in vitro*, and tauroursodeoxycholic acid (TUDCA), which has an antiapoptotic and antioxidizing action, allowed elimination of the amyloid deposits in the majority of the transgenic mice KO/huTTRmet30. This synergic action acts on several tissular stages of the amyloidogenesis and the induced tissular damage [36]; a phase II, open-label study with this combination is ongoing [37▪].

Medicines have been developed to knockdown hepatic synthesis of both mutant and wild-type TTR.

An antisense oligonucleotide (ASO) targeting hepatic mRNA TTR, ISIS-TTR_{Rx}, was identified. When tested in a human TTR transgenic mouse model, ISIS-TTR_{RX} showed a dose-dependent reduction of human TTR (up to >80%) at both the mRNA and protein levels [38]. Liver TTR mRNA and plasma TTR protein levels were also reduced by approximately 80% after 12 weeks of treatment in monkey. ISIS-TTR_{RX} treatment was well tolerated in both rodents and monkeys and is currently under evaluation in a phase 1 clinical trial in normal healthy volunteers [39▪].

ALN-TTR01 is a systemically administered lipid nanoparticle formulation of a small interfering RNA (siRNA) targeting wild-type and all mutant forms of TTR. This formulation delivers the siRNA predominantly to the liver, thereby inhibiting TTR synthesis at the primary site of production. In transgenic mice expressing the human Met30 transgene in a heat shock transcription factor 1 null background, ALN-TTR01 led to a robust reduction of hepatic TTR mRNA levels in the liver and TTR protein levels in the circulation and significant regression of TTR protein in the peripheral nervous system and gut. These results demonstrate the potential therapeutic benefit of ALN-TTR01 for the treatment of transthyretin-mediated amyloidosis (ATTR). Results from a phase I clinical study with ALN-TTR01 demonstrated that administration resulted in statistically significant reductions in serum TTR protein levels, including both wild-type and mutant TTR protein, in ATTR patients. Knockdown of TTR, the disease-causing protein, was found to be dose dependent, rapid, and durable after just a single dose (Coelho *et al.* personal communication).

Enhancers of clearance of amyloid deposits have been developed with monoclonal antibody (Mab) against human serum amyloid P component (hu-SAP), an ubiquitous nonfibrillar plasma glycoprotein in amyloid deposits. Administration of hu-SAPMab to mice with amyloid deposits containing hu-SAP triggers a potent complement-dependent, macrophage-derived giant cell reaction that swiftly removes massive visceral amyloid deposits. This therapy could be applicable to TTR-FAP [40].

De-novo amyloid neuropathy after domino liver transplantation

To compensate for the lack of donors for liver transplantation, livers from FAP patients that are normal except for production of the mutant TTR are proposed for grafting to patients with severe liver diseases, a process called domino liver transplantation (DLT). In a prospective study to assess the risk–benefit ratio of DLT, systemic amyloidosis developed early with amyloid deposits on LSGB 5 years after DLT in half of patients [41▪] or on rectal biopsy in one-third of patients [42].

In DLT recipients, nerve biopsy is crucial [41▪] to prove that the neuropathy is due to amyloidosis and not to other causes [41▪,42]. In a monocentric study of 91 patients who underwent DLT, amyloidosis was proven by nerve biopsy in four of seven cases who developed or had worsened neuropathy [41▪] and other causes in the others. Electrophysiological studies in de-novo amyloid PNP may show axonal neuropathy or may be normal [41▪]. The delay to declaring PNP ranges from 3.5 [41▪] to 9 years [43]. De-novo amyloid neuropathy mimics FAP of early onset [41▪].

LIGHT CHAIN AMYLOID NEUROPATHY

Peripheral neuropathy occurs in about 35% of cases of AL amyloidosis but is a rare presenting symptom. The prototypical presentation is a length-dependent PNP with autonomic dysfunction; but half of patients have atypical presentations including: multifocal neuropathy, painful neuropathy, lumbosacral plexopathy [14▪] or upper limb neuropathy [44], or may mimic CIDP [45]. Careful follow-up of these patients after IVIg treatment should help to reconsider the diagnosis in cases of patient deterioration and elicit a nerve biopsy [9▪▪]. Presence of monoclonal gammopathy or immunoglobulin free lambda LC is suggestive of the diagnosis [14▪].

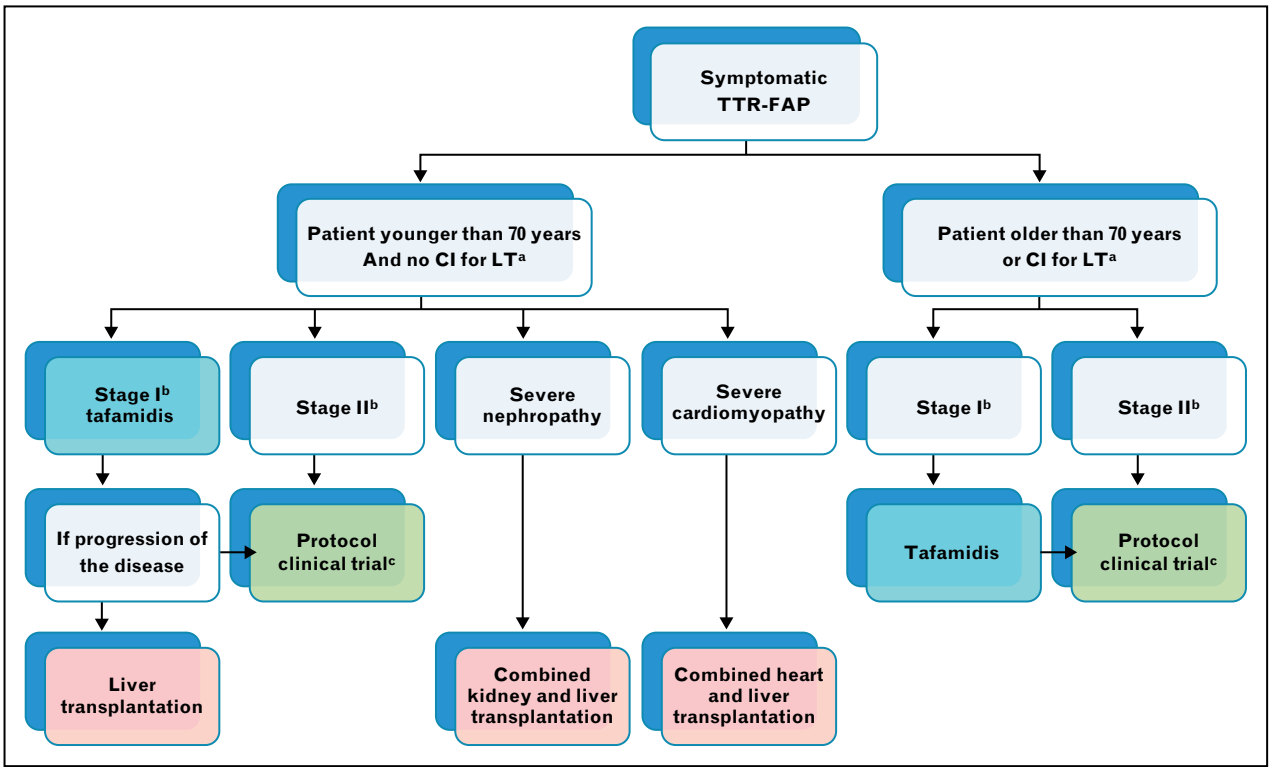

FIGURE 2. Strategy for specific therapy in transthyretin familial amyloidosis with polyneuropathy. TTR-FAP, transthyretin familial amyloidosis with polyneuropathy. [a]Contraindications (CI) for liver transplantation (LT): active and uncontrolled cancer; age over 70 years; cardiac insufficiency. [b]stage I: walking unaided outside; stage II: walking with aid. [c]Protocol clinical trial for combination doxycycline–tauroursodeoxycholic acid, antisense oligonucleotides, small interfering RNA.

Treatments of AL amyloid are directed at destroying the underlying plasma cell clone, which in turn reduces or eliminates the amyloidogenic clonal immunoglobulin LC. High-dose melphalan followed by autologous peripheral blood stem cell transplantation (HDM/SCT) is the main therapy proposed for AL amyloidosis [46▪]. This therapy was successful in two patients with AL amyloid PNP, with improvement of sensory and autonomic neuropathy in conjunction with normalization of serum-free LC [47]. Autonomic neuropathy is an independent adverse determinant of survival in AL amyloid patients who underwent HDM/SCT [48].

CONCLUSION

The diagnosis of amyloid neuropathy must be suspected in progressive cryptogenic neuropathy with many phenotypes even when positive family story, autonomic dysfunction or systemic manifestations are lacking. Appropriate investigations for diagnosis are *TTR* gene sequencing and nerve biopsy or LSGB in referral centers.

Liver transplantation or tafamidis, approved by the EMA for stage 1 TTR-FAP, should be proposed for met30TTR-FAP of early onset. In late-onset TTR-FAP, severe restrictive cardiomyopathy should suggest a combined heart and liver transplantation. In other cases, an antiamyloid medicine protocol should be proposed, including siRNA or ASO (Fig. 2).

Future research should improve methods for early diagnosis and validate new therapies in multicentric clinical trials for both the neuropathy and the cardiomyopathy.

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None.

Conflicts of interest

Consultancy for Alnylam and ISIS; participating in a symposium for Pfizer.

REFERENCES AND RECOMMENDED READING

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- ▪ of special interest
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