



Transthyretin-Related Familial Amyloid Polyneuropathy: In the Light of New Developments

Yeni Gelişmeler Işığında Transtiretin İlişkili Ailevi Amiloid Polinöropatisi

Arman Çakar, Hacer Durmuş Tekçe, Feza Deymeer, Piraye Oflazer Serdaroğlu, Yeşim G. Parman
Istanbul University Istanbul Faculty of Medicine, Department of Neurology, Istanbul, Turkey

Abstract

Transthyretin-related familial amyloid polyneuropathy (TTR-FAP) is caused by gain-of-toxic-function of TTR, which dissociates from its native tetramer form to a monomer form and aggregates in several tissues and organs. Mutations in the TTR gene lead to this amyloidogenic transformation and cause autosomal dominant disease. TTR-FAP typically causes sensorimotor FAP accompanied by autonomic involvement, but considerable phenotypic diversity is noted between different mutation types. In the event of clinical suspicion, TTR gene sequencing and pathologic confirmation are the recommended paths to follow. Significant improvement has been achieved in treating the disease over the past 20 years, starting with liver transplantation, followed by tetramer stabilizers and TTR-lowering therapies. Although there are still some uncertainties in diagnosing and treating TTR-FAP, recent advances are promising, especially in the field of treatment.

Keywords: Amyloidosis, transthyretin, polyneuropathy, genetics, neuropathy

Öz

Transtiretin ilişkili ailevi amiloid polinöropatisi (TTR-FAP), vücutta tetramer formda bulunan TTR'nin monomer hale gelerek toksik özellik kazanması ve çeşitli doku ve organlarda birikmesi sonucunda gelişir. TTR genindeki mutasyonlar, proteine amiloidojenik özellik kazandırmakta ve otozomal dominant geçişli hastalığa neden olmaktadır. TTR-FAP tipik olarak otonom tutulumun eşlik ettiği sensorimotor nöropatiye neden olur, ancak farklı mutasyon tipleri arasında ciddi fenotipik farklılık belirtilmiştir. Klinik şüphe halinde genetik ve patolojik inceleme yapılması gerekmektedir. Son 20 yılda, karaciğer transplantasyonu ile başlayan, tetramer stabilizatörlerin ve TTR yapımını baskılayan ilaçların klinik çalışmalarda ciddi etkisinin gösterilmesi ile devam eden süreçte tedavi açısından önemli yol alınmıştır. Hastalığın tanı ve tedavisinde hala bazı belirsizlikler olmakla birlikte, özellikle tedavi alanındaki son gelişmeler ümit vericidir.

Anahtar Kelimeler: Amiloidoz, transtiretin, polinöropati, genetik, nöropati

Introduction

After being defined in a 37-year-old female as *mal dos pesinos* (foot disease) by Corino Andrade (1,2) approximately 65 years ago, there have been numerous developments in genetics, pathophysiology, and treatment of transthyretin-related familial amyloid polyneuropathy (TTR-FAP), in which amyloid fibrils containing mutant TTR protein deposit in various tissues and organs, especially peripheral nerves. Previously known as prealbumin, the TTR protein carries vitamin A and thyroxine

in blood. TTR, a 127 amino acid protein, which is encoded on chromosome 18, is primarily synthesized by the liver and choroid plexus, small intestine, and retinal pigment epithelium. Four monomers come together to form the tetramer structure of the protein. TTR loses its stable structure as a result of mutations in the TTR gene and transforms into undissolved amyloid fibrils (3). More than 120 mutations have so far been identified that cause this autosomal dominant inherited disease (4). The distribution of these mutations varies in different geographic regions, and the clinical

Address for Correspondence/Yazışma Adresi: Arman Çakar MD, Istanbul University Istanbul Faculty of Medicine, Department of Neurology, Istanbul, Turkey
Phone: +90 212 414 20 00/32571 E-mail: arrmmaan@hotmail.com ORCID ID: orcid.org/0000-0002-8129-4172

Received/Geliş Tarihi: 15.05.2016 **Accepted/Kabul Tarihi:** 21.08.2016

©Copyright 2017 by Turkish Neurological Society
Turkish Journal of Neurology published by Galenos Publishing House.

features vary due to the type of mutation. The most common mutation worldwide is the substitution of valine for methionine at position 30 (Val30Met), which is also the most common mutation in Portugal where the disease was first described. Val30Met is also the most common mutation in other endemic countries including Sweden and Japan, and its prevalence increases up to a level of 1/500 in Portugal (5). However, the distribution of mutations is heterogeneous in the rest of the world.

Diagnosis, Clinical Course, and Differential Diagnosis

The classic symptoms in the early stages of the disease are sensory loss, predominantly of distal parts of the lower extremities, and neuropathic pain. Motor and autonomic impairment are added with progression of the disease. Sensorial symptoms reach proximal parts of extremities and the anterior part of the trunk (1). Motor impairment affects distal parts of the lower extremities first, and then fine work of upper extremities. Autonomic impairment presents with orthostatic hypotension, impotence, neurogenic bladder, diarrhea and constipation, and may be fatal by causing weight loss and cachexia in late stages of the disease (6).

Impairments of the cardiac, gastrointestinal, and urinary systems, eyes, and central nervous system (CNS) are also possible during the course of the disease. Cardiac impairment is characterized by the deposition of amyloidogenic TTR in the ventricles, causing thickening of the ventricular walls, which then causes diastolic dysfunction and arrhythmias. Systolic dysfunction and low ejection fraction are often added later (7). Ocular involvement may include vitreous opacities, which could even require vitrectomy, glaucoma, and rarely dry eye syndrome (8). Urinary involvement often affects patients in late stages of the disease, but microalbuminuria may be the first finding of a manifest nephropathy. The occurrence of kidney failure is related with poor prognosis (9). Amyloid accumulation in the CNS includes leptomeningeal involvement and accumulation in the media and adventitia of small and medium-diameter arteries, and veins of the cerebral cortex. The pathologic, clinical, and imaging features are different from classic amyloid angiopathy. CNS involvement includes cerebral infarctions and hemorrhages, subarachnoid hemorrhages, transient ischemic attack-like events, hydrocephalus, spastic paraparesis, dementia, and ataxia. Hoarseness due to vocal cord involvement, spinal stenosis, and hypothermia are other rare involvements of the disease (10). Different mutation types cause different clinical features: dominant motor involvement with Tyr78Phe mutations, initiation of the disease from the upper extremities with Leu58His mutations, and initiation of the disease with Carpal Tunnel syndrome with Glu89Gln mutation are some examples (6,11). Presentation with isolated cardiac involvement but very mild neurologic involvement with Val122Ile mutations, and leptomeningeal amyloidosis with Asp18Gly, Ala25Thr, and Gly53Glu mutations have also been reported (6,12,13,14). These clinical differences vary between different mutations, and there are also phenotypic differences between family members with the same mutation (1).

This clinical heterogeneity may complicate the diagnosis of sporadic cases in patients who have no family history and who live in non-endemic areas. It can take 4 years for these patients to be diagnosed from the beginning of symptom onset (15). Chronic inflammatory

demyelinating polyneuropathy (CIDP) is at the top of the differential diagnosis list; 50% of patients with TTR-FAP can initially be misdiagnosed as having CIDP (16). Some patients with TTR-FAP could have high levels of cerebrospinal fluid protein and demyelination secondary to axonal damage could electrophysiologically mimic CIDP, which are the main reasons for misdiagnosis (17). In the event of unresponsiveness to immunologic treatment in these patients, TTR-FAP should be considered. AL-amyloidosis is another misdiagnosis, because monoclonal gammopathy, which is frequent in older patients, can be mistakenly interpreted as amyloidogenic. Length-dependent polyneuropathy with symptoms of autonomic involvement in patients who do not have diabetes mellitus suggests the diagnosis of TTR-FAP and prevents misdiagnosis. Other highly suggestive features of TTR-FAP are:

- Length-dependent neuropathy with findings of small fiber neuropathy, disturbances of pain and temperature senses, and preserved sense of touch;
- Patients with family members who have both neuropathic findings and heart failure;
- Carpal Tunnel syndrome that recurs after surgery in male patients without an obvious cause;
- Ventricular hypertrophy without hypertension;
- Symptoms of autonomic involvement including erectile dysfunction, neurogenic bladder, and especially disturbances of gastrointestinal motility that cannot be explained;
- Unexplained glaucoma and vitreous opacities.

In the presence of the above mentioned findings, a mutation can be detected using TTR gene sequencing. However, the detection of a mutation does not directly show the existence of clinical amyloidosis (18). Conversely, not detecting a mutation does not rule out the existence of amyloidosis, except TTR. Therefore, amyloid accumulation in tissues should be observed for a histopathologic diagnosis (Figure 1). Abdominal wall fat pad, gingival, salivary gland, and rectal biopsies are preferred to nerve biopsy because of the ease of access to these tissues and having low complication risks (19). In the event of development of Carpal Tunnel syndrome due to the disease, the Carpal Tunnel ligament can be used as an alternative tissue for diagnosis. The most commonly used biopsies, abdominal wall fat pad and salivary gland, have a sensitivity of 73-83% in the diagnosis of TTR-FAP (20). A negative biopsy does not rule out the diagnosis of TTR-FAP because of segmental involvement (21).

After the diagnosis, staging of the disease must be performed to follow up and choose from potential treatment options. Staging is also important to show objective benefit in drug studies. The most commonly used scoring methods are FAP staging and polyneuropathy disability (PND) scoring (Table 1).

FAP staging is an important factor in choosing an appropriate treatment option because the benefits of disease modifying medications in patients with stage 3 disease are controversial. Rather than these 2 scoring methods showing functional states of the patients, there are other scoring methods including the Neuropathy Impairment Score (NIS), which evaluates the severity of neuropathy through examinations and paraclinical tests such as "Quantitative Sensory Testing", "NIS-Lower Limbs" (NIS-LL), and the "Modified NIS+7" (mNIS+7). The latter scoring methods are especially used to evaluate the efficacy of newly developed medications. Heart rate variability to test autonomic

involvement, echocardiography, rhythm Holter, serum brain-type natriuretic peptide (proBNP) level, ophthalmologic examination, body mass index, urinary ultrasonography, routine blood and urine analyses repeated at least at 6-month intervals can give an idea about the progression of the disease (1).

Treatment

Symptomatic Treatment

Besides treatments including liver transplantation and disease-modifying medications developed over the last 20 years, symptomatic treatment obviously improves a patient's quality of life. Table 2 shows symptomatic treatment options.

Liver Transplantation

Known as a fatal disease, the first and an important development in the treatment of TTR-FAP was orthotopic liver transplantation, which was shown to have prognostic effects on TTR-FAP (22). Liver transplantation was performed for years in more than 2000 patients and as a result of removing the source of TTR, there was a 90% decrease in serum levels of TTR (23). The five-year survival rate after transplantation is approximately 90% in patients with Val30Met, and 60% in patients with other mutations (24). Apart from the type of mutation, age, disease

stage, autonomic dysfunction, cardiomyopathy, and malnutrition are other factors that affect the prognosis after transplantation. Although transplantation is an effective treatment option, the lack of donors, and the need for long-term immunosuppressive treatments for and complications of surgery limit its applicability (25). The one-year mortality rate is 7-25% and the main causes of death are infections and hepatic artery thrombosis (26,27). Lymphoproliferative diseases and renal failure are important long-term complications, but some studies showed that progression of nephrologic involvement decreases after transplantation (28,29). Involvement of the CNS and eyes is resistant to transplantation because production of mutant TTR continues in the choroid plexus and retinal pigment epithelium (30).

Disease progression continues in some patients after liver transplantation, especially cardiac impairment, which suggests the need for performing simultaneous heart-liver transplantation. Although this procedure seems to carry greater risk, mortality rates are similar to isolated liver transplantation (31). Isolated heart transplantation in patients with Val122Ile mutation who only present with cardiomyopathy has the same 5-year mortality rate as heart transplantations performed for other reasons (32).

As a result of the increase in liver transplantations for this indication, livers from patients with TTR-FAP were considered as donor organs for patients with chronic liver diseases in the mid-nineties; this procedure was called domino liver transplantation.

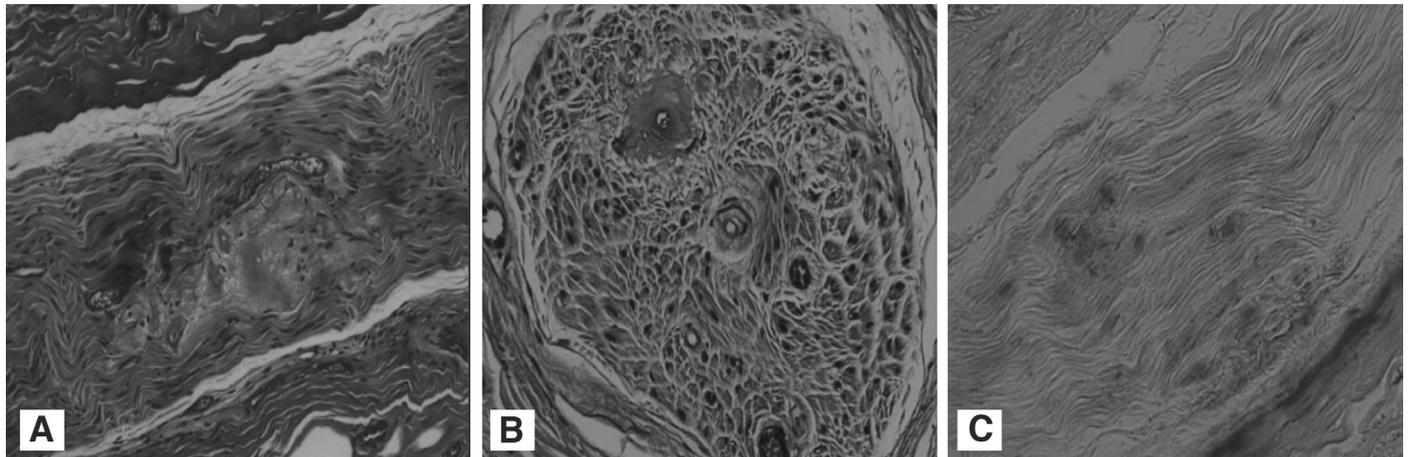


Figure 1. Cross-section of a nerve biopsy. A) Endoneurial amyloid deposits are seen (Hematoxylin&eosin x20), B) Perivascular amyloid deposits in the endoneurium are seen (Hematoxylin&eosin x20), C) Endoneurial amyloid deposits are seen (Crystal violet x20) (Taken from the archives of the Coşkun Özdemir Neuromuscular Diseases Research Laboratory).

Table 1. Staging options in transthyretin-related familial amyloid polyneuropathy

FAP staging		PND score	
Stage	Symptom	Score	Symptom
0	Asymptomatic	1	Only sensory disturbances
1	Symptomatic but ambulatory without aid	2	Motor impairment but ambulatory without aid
2	Ambulatory with aid	3A	Walking with the help of one stick
3	Wheelchair-bound	3B	Walking with the help of two sticks
		4	Wheelchair-bound

FAP: Familial amyloid polyneuropathy, PND: Polyneuropathy disability

When the natural course of the disease is considered, it was predicted that the disease would recur 20-30 years after transplantation (33). However, long-term follow-up showed that the time to develop the disease was shorter; TTR amyloidosis recurred in the same patients just 10 years after transplantation. In this group of patients, re-transplantation was shown to carry greater risk. In addition, there are no data about the applicability of disease-modifying medications (34).

New Treatment Options

Although liver transplantation is an effective treatment option, it cannot be used in the late stage of the disease, it has limited benefit in patients with non-Val30Met mutations, and it has major perioperative and postoperative risks, all of which require the development of new treatment options. In the last 10 years, with the development of new medications that change the course of the disease, much progress has been made in treatment, and still there are several drug trials underway. Current medications aim to prevent TTR from becoming amyloidogenic by stabilizing the tetramer structure of TTR and suppressing TTR production in the liver. Options such as monoclonal antibodies aimed at TTR are expected to arise in the future (35).

Tafamidis

Tafamidis stabilizes the tetramer structure of TTR and effects by binding to TTR's thyroxine binding site. Tafamidis has been approved in Europe, Japan, and South American countries. After the *in vitro* effects of tafamidis were observed, phase 2 and 3 trials were performed. In the pioneer study called Fx-005, more than 2 points of increase in NIS-LL were found to be significantly higher in the placebo group compared with patients who took 20 mg tafamidis per day (60-38%). Patients with Val30Met mutations

who were in stage 1 and followed up for 18 months were included in the study (36). Similar results for quality of life and body mass index were shown, but no statistical significance was found for the primary endpoint "intention-to-treat." In the 12-month extended open-label study, stabilization in NIS-LL persisted, changes in NIS-LL decreased, and quality of life measures were improved in patients who were switched from placebo to tafamidis (37). Shown as a safe drug in studies, diarrhea and urinary system infections were reported as adverse events. Although tafamidis was effective in patients with stage 1 disease, a study performed in patients with Val30Met mutations with late-stage disease showed progression in NIS (38). The decrease in serum levels of TTR, which was not measured in the pioneer study, was found as 95% in a study performed in 21 patients with non-Val30Met mutations (39).

A single-center study without a control group performed in 98 patients to evaluate the effects of tafamidis on nephropathy showed that no patients had newly developed albuminuria and the urine albumin/creatinine ratio (UACR) persisted after 12 months of follow up. The UACR also decreased and glomerular filtration rate persisted in patients with proteinuria (UACR >300 mg/d); however, there was no control group in the study and the effect of tafamidis on nephropathy could not be accurately shown (40).

An ongoing phase 3 clinical trial was initiated (NCT01994889) to evaluate and compare the effects of 20 mg/d and 80 mg/d tafamidis in patients with Val122Ile mutations and dominant cardiac involvement.

Diflunisal

Diflunisal, a nonsteroidal anti-inflammatory drug, has been available on the market for 40 years and is often used in the treatment of rheumatic diseases. *In vitro* studies showed that it affects TTR's thyroxine binding site, like tafamidis (41). In light of these data, a phase 3 study was initiated in 2006. One hundred thirty patients with a mean age of 59.7 years were randomized into two groups. The first group was given placebo and the second was given 250 mg diflunisal twice a day for 24 months. Approximately 50% of the patients had non-Val30Met mutations and also patients with late-stage disease with higher PND scores were included in the study. The average increase in NIS+7 was 8.7 in the diflunisal group, whereas it was 25 in the placebo group (42). Nevertheless, 42% of patients in the diflunisal group discontinued the drug in the 24-month follow-up. The cardiac effects of diflunisal were also evaluated and it was shown that there was no difference between the groups in terms of left ventricular wall thickening, but in a subgroup with higher BNP levels, diflunisal decreased left ventricular wall thickening compared with placebo. Although ineffectiveness was found to be the most frequent cause of drug discontinuation in that study, adverse events including thrombocytopenia, deterioration of renal function and gastrointestinal bleeding were reported in some patients in other studies. This study continued in the long term as an open-label study and it was found that the clinical effects of diflunisal were sustained after 2 years of treatment. However, the slow deterioration of clinical symptoms in most patients and the profile of adverse events indicated that future studies were required to test diflunisal's place in patients with FAP-TTR with early-stage disease (43). There are no data about the use of other treatment options in patients with late-stage disease; diflunisal can be used in these patients.

Table 2. Symptomatic treatment options in transthyretin-related familial amyloid polyneuropathy

Complaint	Treatment
Neuropathic pain	Pregabalin, gabapentin, amitriptyline, duloxetine
Orthostatic hypotension	Fludrocortisone, midodrine, droxidopa, compression stockings
Diarrhea	Metoclopramide, loperamide
Carpal Tunnel syndrome	Local corticosteroid injection, surgery
Arrhythmia	Antiarrhythmic medications, pacemaker implantation
Heart failure	Diuretics, ACE inhibitors
Renal failure	Hemodialysis
Vitreous opacities, glaucoma	Vitrectomy, trabeculectomy
Urinary incontinence	Bethanechol, distigmine
Sexual dysfunction	Sildenafil, tadalafil

ACE: Angiotensin-converting-enzyme

Doxycycline+Tauroursodeoxycholic Acid (TUDCA)

In vitro studies showed that the combination of doxycycline, an antibiotic from the tetracycline group, and TUDCA, a bile acid, decreases amyloid accumulation in tissues (44). In a phase 2 trial, 100 mg doxycycline twice per day and 250 mg TUDCA three times per day were shown to be safe. Flushing and dyspeptic symptoms due to doxycycline were the most frequent adverse events. Due to the preliminary results of that study, which included 20 patients (one patient had a domino transplantation), patients were stable in terms of neurologic and cardiac status (45).

Patisiran (ALN-TTR02)

Patisiran, a lipid-encapsulated small-interfering RNA molecule, aims to bind TTR's mRNA and prevent the production of the protein. It has a similar mechanism of action with liver transplantation, but differently, it inhibits the synthesis of both mutant and non-mutant (wild type) TTR. It prevents cardiac worsening that occurs after transplantation by preventing the accumulation of "wild type" TTR. Preclinical studies showed a decrease in serum and tissue levels of TTR after administration of patisiran (46). In a phase 1 trial, the decrease in serum levels of TTR was 94%, which was similar to liver transplantation (47). No adverse events were reported, except reactions in the area of injection. In a phase 2 study that included 29 patients who were in stage 1 or 2, 0.3 mg/kg patisiran was administered intravenously once every 3 weeks and an average 84% decrease in serum TTR levels was detected. The study then went on as open-label and an average 2.5 points decrease was achieved in mNIS+7 in 27 patients after 12 months' follow-up. When compared with the approximately 10-18 points increase in the natural course of the disease, it was concluded that biochemical wellness reflected the clinical course. The most frequent adverse events were infusion-related reactions, nasopharyngitis, and flushing; no adverse events were reported to cause drug discontinuation (48). In view of these studies with encouraging data, a phase 3 trial (APOLLO) of patisiran, in which our clinic was also involved, has been initiated and planned to last 18 months.

In addition, a phase 3 trial (ENDEAVOUR) of revusiran, a subcutaneous form of patisiran conjugated with N-acetylgalactosamine, in patients with TTR-FAP-related cardiac involvement has been initiated (49). Patients will be administered 500 mg/d revusiran subcutaneously for 5 days and then 500 mg per week. These patients will then be compared with placebo in terms of 6-minute walk test and changes in serum TTR levels.

ISIS- Transthyretin_{Rx}

ISIS-TTR_{Rx}, an antisense oligonucleotide inhibitor, binds to the TTR mRNA's 3' end, which is not translated, and catalyzes the degradation of RNA via RNAase (50). ISIS-TTR_{Rx} was shown to decrease serum levels of TTR by 80% in transgenic mice with Ile84Ser mutations (51). It was used subcutaneously in the phase 1 trial and was shown to be safe except for minor adverse events including pain related with

injections and somnolence. In the phase 3 trial (NCT02175004), which is continuing, patients taking 300 mg/d ISIS-TTR_{Rx} subcutaneously for 3 days followed by 300 mg per week will be compared with placebo in terms of mNIS+7 and quality of life scales after 65 weeks' follow-up.

Intraventricular administration of ISIS-TTR_{Rx} in transgenic mice was shown to decrease TTR levels in the choroid plexus. This data is promising with regards to using the drug in leptomeningeal amyloidosis, in which no medication has yet shown to be effective. However, there are no current studies pertaining to this indication (52).

Management

An algorithm is required due to the rapid increase in treatment options of TTR-FAP in recent years. Centers in Europe reached a consensus on the treatment of FAP-TTR in 2015 (Table 3).

Stage 0	Follow-up according to the type of mutation and patient's clinical status
	- Tafamidis
Stage 1	- If progression continues, liver transplantation or one of the phase 3 trials
	- Diflunisal
Stage 2	- One of the phase 3 trials
	- There is no treatment approved
Stage 3	- Supporting treatment, if possible one of the phase 3 trials

Besides these groups of patients, simultaneous liver-kidney transplantation in patients with severe nephropathy, and simultaneous heart-liver transplantation in patients with severe cardiac involvement are recommended (53).

Conclusion

TTR-FAP is a rare but life-threatening disease. The development of new treatment options is promising, but to gain maximum benefit, early diagnosis and commencement of treatment are required. Recognition of the disease by cardiologists, nephrologists, neurologists, and even ophthalmologists will significantly decrease the morbidity and mortality rates of the disease.

Ethics

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: A.Ç., H.D.T., F.D., P.O.S., Y.G.P., Concept: A.Ç., H.D.T., Y.G.P., Design: A.Ç., H.D.T., Y.G.P., Data Collection or Processing: A.Ç., H.D.T., F.D., P.O.S., Y.G.P., Analysis or Interpretation: A.Ç., H.D.T., Y.G.P., Literature Search: A.Ç., H.D.T., Y.G.P., Writing: A.Ç., H.D.T., Y.G.P.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

References

- Ando Y, Coelho T, Berk JL, Cruz MW, Ericzon BG, Ikeda S, Lewis WD, Obici L, Plante-Bordeneuve V, Rapezzi C, Said G, Salvi F. Guideline of transthyretin-related hereditary amyloidosis for clinicians. *Orphanet J Rare Dis* 2013;8:31.
- Andrade C. A peculiar form of peripheral neuropathy; familiar atypical generalized amyloidosis with special involvement of the peripheral nerves. *Brain* 1952;75:408-427.
- Adams D, Theaudin M, Cauquil C, Algalarrondo V, Slama M. FAP neuropathy and emerging treatments. *Curr Neurol Neurosci Rep* 2014;14:435.
- Benson MD, Kincaid JC. The molecular biology and clinical features of amyloid neuropathy. *Muscle Nerve* 2007;36:411-423.
- Ando Y, Nakamura M, Araki S. Transthyretin-related familial amyloidotic polyneuropathy. *Arch Neurol* 2005;62:1057-1062.
- Sekijima Y, Yoshida K, Tokuda T, Ikeda S. Familial Transthyretin Amyloidosis. In: Pagon RA, Adam MP, Ardinger HH, Wallace SE, Amemiya A, Bean LJH, Bird TD, Fong CT, Mefford HC, Smith RJH, Stephens K, editors. *Gene Reviews(R)*: Seattle (WA), 1993.
- Ruberg FL, Berk JL. Transthyretin (TTR) cardiac amyloidosis. *Circulation* 2012;126:1286-1300.
- Rousseau A, Kaswin G, Adams D, Cauquil C, Theaudin M, Mincheva Z, M'Garrech M, Labetoulle M, Barreau E. Ocular involvement in familial amyloid polyneuropathy. *J Fr Ophtalmol* 2013;36:779-788.
- Lobato L, Rocha A. Transthyretin amyloidosis and the kidney. *Clin J Am Soc Nephrol* 2012;7:1337-1346.
- Durmuş-Tekçe H, Matur Z, Mert Atmaca M, Poda M, Çakar A, Hıdır Ulaş Ü, Oflazer-Serdaroğlu P, Deymeer F, Parman YG. Genotypic and phenotypic presentation of transthyretin-related familial amyloid polyneuropathy (TTR-FAP) in Turkey. *Neuromuscul Disord* 2016;26:441-446.
- Riboldi G, Del Bo R, Ranieri M, Magri F, Sciacco M, Moggio M, Bresolin N, Corti S, Comi GP. Tyr78Phe Transthyretin Mutation with Predominant Motor Neuropathy as the Initial Presentation. *Case Rep Neurol* 2011;3:62-68.
- Yamashita T, Hamidi Asl K, Yazaki M, Benson MD. A prospective evaluation of the transthyretin Ile122 allele frequency in an African-American population. *Amyloid* 2005;12:127-130.
- Ellie E, Camou F, Vital A, Rummens C, Grateau G, Delpuch M, Valleix S. Recurrent subarachnoid hemorrhage associated with a new transthyretin variant (Gly53Glu). *Neurology* 2001;57:135-137.
- Parman Y, Adams D, Obici L, Galan L, Guerguelcheva V, Suhr OB, Coelho T; European Network for TTR-FAP (ATTReuNET). Sixty years of transthyretin familial amyloid polyneuropathy (TTR-FAP) in Europe: where are we now? A European network approach to defining the epidemiology and management patterns for TTR-FAP. *Curr Opin Neurol* 2016;29(Suppl 1):3-13.
- Plante-Bordeneuve V, Ferreira A, Lulu T, Zaros C, Lacroix C, Adams D, Said G. Diagnostic pitfalls in sporadic transthyretin familial amyloid polyneuropathy (TTR-FAP). *Neurology* 2007;69:693-698.
- Koike H, Hashimoto R, Tomita M, Kawagashira Y, Iijima M, Tanaka F, Sobue G. Diagnosis of sporadic transthyretin Val30Met familial amyloid polyneuropathy: a practical analysis. *Amyloid* 2011;18:53-62.
- Conceicao I, Gonzalez-Duarte A, Obici L, Schmidt HH, Simoneau D, Ong ML, Amass L. "Red-flag" symptom clusters in transthyretin familial amyloid polyneuropathy. *J Peripher Nerv Syst* 2016;21:5-9.
- Obici L, Kuks JB, Buades J, Adams D, Suhr OB, Coelho T, Kyriakides T; European Network for European Network for TTR-FAP (ATTReuNET). Recommendations for presymptomatic genetic testing and management of individuals at risk for hereditary transthyretin amyloidosis. *Curr Opin Neurol* 2016;29(Suppl 1):27-35.
- Sekijima Y. Transthyretin (ATTR) amyloidosis: clinical spectrum, molecular pathogenesis and disease-modifying treatments. *J Neurol Neurosurg Psychiatry* 2015;86:1036-1043.
- Van G, Hazenberg BP, Bijzet J, van Rijswijk MH. Diagnostic accuracy of subcutaneous abdominal fat tissue aspiration for detecting systemic amyloidosis and its utility in clinical practice. *Arthritis Rheum* 2006;54:2015-2021.
- Simmons Z, Blaivas M, Aguilar AJ, Feldman EL, Bromberg MB, Towfighi J. Low diagnostic yield of sural nerve biopsy in patients with peripheral neuropathy and primary amyloidosis. *J Neurol Sci* 1993;120:60-63.
- Herlenius G, Wilczek HE, Larsson M, Ericzon BG; Familial Amyloidotic Polyneuropathy World Transplant Registry. Ten years of international experience with liver transplantation for familial amyloidotic polyneuropathy: results from the Familial Amyloidotic Polyneuropathy World Transplant Registry. *Transplantation* 2004;77:64-71.
- Yamamoto S, Wilczek HE, Nowak G, Larsson M, Oksanen A, Iwata T, Gjertsen H, Söderdahl G, Wikström L, Ando Y, Suhr OB, Ericzon BG. Liver transplantation for familial amyloidotic polyneuropathy (FAP): a single-center experience over 16 years. *Am J Transplant* 2007;7:2597-2604.
- Carvalho A, Rocha A, Lobato L. Liver transplantation in transthyretin amyloidosis: issues and challenges. *Liver Transpl* 2015;21:282-292.
- Wilczek HE, Larsson M, Ericzon BG; FAPWTR. Long-term data from the Familial Amyloidotic Polyneuropathy World Transplant Registry (FAPWTR). *Amyloid* 2011;18(Suppl 1):193-195.
- Adams D. Recent advances in the treatment of familial amyloid polyneuropathy. *Ther Adv Neurol Disord* 2013;6:129-139.
- Bispo M, Marcelino P, Freire A, Martins A, Mourao L, Barroso E. High incidence of thrombotic complications early after liver transplantation for familial amyloidotic polyneuropathy. *Transpl Int* 2009;22:165-171.
- Nowak G, Suhr OB, Wikström L, Wilczek H, Ericzon BG. The long-term impact of liver transplantation on kidney function in familial amyloidotic polyneuropathy patients. *Transpl Int* 2005;18:111-115.
- Jain A, Nalesnik M, Reyes J, Pokharna R, Mazariegos G, Green M, Eghtesad B, Marsh W, Cacciarelli T, Fontes P, Abu-Elmagd K, Sindhi R, Demetris J, Fung J. Posttransplant lymphoproliferative disorders in liver transplantation: a 20-year experience. *Ann Surg* 2002;236:429-436.
- Yazaki M, Tokuda T, Nakamura A, Higashikata T, Koyama J, Higuchi K, Harihara Y, Baba S, Kametani F, Ikeda S. Cardiac amyloid in patients with familial amyloid polyneuropathy consists of abundant wild-type transthyretin. *Biochem Biophys Res Commun* 2000;274:702-706.
- Nelson LM, Penninga L, Sander K, Hansen PB, Villadsen GE, Rasmussen A, Gustafsson F. Long-term outcome in patients treated with combined heart and liver transplantation for familial amyloidotic cardiomyopathy. *Clin Transplant* 2013;27:203-209.
- Dubrey SW, Burke MM, Hawkins PN, Banner NR. Cardiac transplantation for amyloid heart disease: the United Kingdom experience. *J Heart Lung Transplant* 2004;23:1142-1153.
- Schmidt HH, Nashan B, Pröpsting MJ, Nakazato M, Flemming P, Kubicka S, Böker K, Pichlmayr R, Manns MP. Familial Amyloidotic Polyneuropathy: domino liver transplantation. *J Hepatol* 1999;30:293-298.
- Zarrinpar A, Hong JC. What is the prognosis after retransplantation of the liver? *Adv Surg* 2012;46:87-100.
- Obayashi K, Tasaki M, Jono H, Ueda M, Shinriki S, Misumi Y, Yamashita T, Oshima T, Nakamura T, Ikemizu S, Anan I, Suhr O, Ando Y. Impact of antibodies against amyloidogenic transthyretin (ATTR) on phenotypes of patients with familial amyloidotic polyneuropathy (FAP) ATTR Valine30Methionine. *Clin Chim Acta* 2013;419:127-131.
- Coelho T, Maia LF, Martins da Silva A, Waddington Cruz M, Plante-Bordeneuve V, Lozeron P, Suhr OB, Campistol JM, Conceicao IM, Schmidt HH, Trigo P, Kelly JW, Labaudiniere R, Chan J, Packman J, Wilson A, Grogan DR. Tafamidis for transthyretin familial amyloid polyneuropathy: a randomized, controlled trial. *Neurology* 2012;79:785-792.
- Coelho T, Maia LF, da Silva AM, Cruz MW, Plante-Bordeneuve V, Suhr OB, Conceicao I, Schmidt HH, Trigo P, Kelly JW, Labaudiniere R, Chan J, Packman J, Grogan DR. Long-term effects of tafamidis for the treatment of transthyretin familial amyloid polyneuropathy. *J Neurol* 2013;260:2802-2814.
- Lozeron P, Theaudin M, Mincheva Z, Ducot B, Lacroix C, Adams D; French Network for FAP(CORNAMYL). Effect on disability and safety of Tafamidis in late onset of Met30 transthyretin familial amyloid polyneuropathy. *Eur J Neurol* 2013;20:1539-1545.
- Merlini G, Plante-Bordeneuve V, Judge DP, Schmidt H, Obici L, Perlini S, Packman J, Tripp T, Grogan DR. Effects of tafamidis on transthyretin stabilization and clinical outcomes in patients with non-Val30Met transthyretin amyloidosis. *J Cardiovasc Transl Res* 2013;6:1011-1020.
- Öztürk C, Erdoğan A, Durmuş M, Uğur AL, Kılıçarslan FA, Erden I. Highly soluble 3,4-(dimethoxyphenylthio) substituted phthalocyanines: synthesis, photophysical and photochemical studies. *Spectrochim Acta A Mol Biomol Spectrosc* 2012;86:423-431.

41. Miller SR, Sekijima Y, Kelly JW. Native state stabilization by NSAIDs inhibits transthyretin amyloidogenesis from the most common familial disease variants. *Lab Invest* 2004;84:545-552.
42. Berk JL, Suhr OB, Obici L, Sekijima Y, Zeldenrust SR, Yamashita T, Heneghan MA, Gorevic PD, Litchy WJ, Wiesman JF, Nordh E, Corato M, Lozza A, Cortese A, Robinson-Papp J, Colton T, Rybin DV, Bisbee AB, Ando Y, Ikeda S, Seldin DC, Merlini G, Skinner M, Kelly JW, Dyck PJ; Diflunisal Trial Consortium. Repurposing diflunisal for familial amyloid polyneuropathy: a randomized clinical trial. *JAMA* 2013;310:2658-2667.
43. Sekijima Y, Tojo K, Morita H, Koyama J, Ikeda S. Safety and efficacy of long-term diflunisal administration in hereditary transthyretin (ATTR) amyloidosis. *Amyloid* 2015;22:79-83.
44. Cardoso I, Martins D, Ribeiro T, Merlini G, Saraiva MJ. Synergy of combined doxycycline/TUDCA treatment in lowering Transthyretin deposition and associated biomarkers: studies in FAP mouse models. *J Transl Med* 2010;8:74.
45. Obici L, Cortese A, Lozza A, Lucchetti J, Gobbi M, Palladini G, Perlini S, Saraiva MJ, Merlini G. Doxycycline plus tauroursodeoxycholic acid for transthyretin amyloidosis: a phase II study. *Amyloid* 2012;19(Suppl 1):34-36.
46. Butler JS, Chan A, Costelha S, Fishman S, Willoughby JL, Borland TD, Milstein S, Foster DJ, Goncalves P, Chen Q, Qin J, Bettencourt BR, Sah DW, Alvarez R, Rajeev KG, Manoharan M, Fitzgerald K, Meyers RE, Nochur SV, Saraiva MJ, Zimmermann TS. Preclinical evaluation of RNAi as a treatment for transthyretin-mediated amyloidosis. *Amyloid* 2016;23:109-118.
47. Coelho T, Adams D, Silva A, Lozeron P, Hawkins PN, Mant T, Perez J, Chiesa J, Warrington S, Tranter E, Munisamy M, Falzone R, Harrop J, Cehelsky J, Bettencourt BR, Geissler M, Butler JS, Sehgal A, Meyers RE, Chen Q, Borland T, Hutabarat RM, Clausen VA, Alvarez R, Fitzgerald K, Gamba-Vitalo C, Nochur SV, Vaishnav AK, Sah DW, Gollob JA, Suhr OB. Safety and efficacy of RNAi therapy for transthyretin amyloidosis. *N Engl J Med* 2013;369:819-829.
48. Suhr OB, Coelho T, Buades J, Pouget J, Conceicao I, Berk J, Schmidt H, Waddington-Cruz M, Campistol JM, Bettencourt BR, Vaishnav A, Gollob J, Adams D. Efficacy and safety of patisiran for familial amyloidotic polyneuropathy: a phase II multi-dose study. *Orphanet J Rare Dis* 2015;10:109.
49. Nair JK, Willoughby JL, Chan A, Charisse K, Alam MR, Wang Q, Hoekstra M, Kandasamy P, Kel'in AV, Milstein S, Taneja N, O'Shea J, Shaikh S, Zhang L, van der Sluis RJ, Jung ME, Akinc A, Hutabarat R, Kuchimanchi S, Fitzgerald K, Zimmermann T, van Berkel TJ, Maier MA, Rajeev KG, Manoharan M. Multivalent N-acetylgalactosamine-conjugated siRNA localizes in hepatocytes and elicits robust RNAi-mediated gene silencing. *J Am Chem Soc* 2014;136:16958-16961.
50. Benson MD, Kluve-Beckerman B, Zeldenrust SR, Siesky AM, Bodenmiller DM, Showalter AD, Sloop KW. Targeted suppression of an amyloidogenic transthyretin with antisense oligonucleotides. *Muscle Nerve* 2006;33:609-618.
51. Ackermann EJ, Guo S, Boonen S, Alvarado L, Benson M, Hughes S, Monia BP. Clinical development of an antisense therapy for the treatment of transthyretin-associated polyneuropathy. *Amyloid* 2012;19(Suppl 1):43-44.
52. Benson MD, Smith RA, Hung G, Kluve-Beckerman B, Showalter AD, Sloop KW, Monia BP. Suppression of choroid plexus transthyretin levels by antisense oligonucleotide treatment. *Amyloid* 2010;17:43-49.
53. Adams D, Suhr OB, Hund E, Obici L, Tournev I, Campistol JM, Slama MS, Hazenberg BP, Coelho T; European Network for TTR-FAP (ATTReNET). First European consensus for diagnosis, management, and treatment of transthyretin familial amyloid polyneuropathy. *Curr Opin Neurol* 2016;29(Suppl 1):14-26.