

# We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

6,900

Open access books available

185,000

International authors and editors

200M

Downloads

Our authors are among the

154

Countries delivered to

TOP 1%

most cited scientists

12.2%

Contributors from top 500 universities



WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index  
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?  
Contact [book.department@intechopen.com](mailto:book.department@intechopen.com)

Numbers displayed above are based on latest data collected.  
For more information visit [www.intechopen.com](http://www.intechopen.com)



# Neurological Manifestations of Transthyretin-Related Amyloidosis

*Kourosh Rezania and Laleh Saadat*

## Abstract

Transthyretin related amyloidosis (ATTR) results from the tissue deposition of misfolded mutant or wild-type transthyretin (TTR). Involvement of nervous system often heralds the onset of ATTR. Familial ATTR is because of mutations in the TTR gene which lead to destabilization of the tetrameric structure of TTR and generation of amyloidogenic monomers, tissue deposition of which causes end organ injury specially neuropathy and cardiomyopathy. Peripheral neuropathy is typically axonal with early involvement of the autonomic nerves. Wild-type TTR (ATTRwt), is a common cause of cardiomyopathy in the elderly and may play a role in the pathogenesis of carpal tunnel syndrome and spinal stenosis in that age group. Diagnosis of ATTR is made by demonstrating tissue amyloid deposits, then proving that the amyloid deposits consist of mutant or wild-type TTR, which necessitates assessment of TTR gene sequencing. Disease modifying treatments have become available for ATTR through liver transplantation, stabilization of the TTR molecule (diflunisal and tafamidis) and suppressing the gene expression of TTR (inotersen and patisiran).

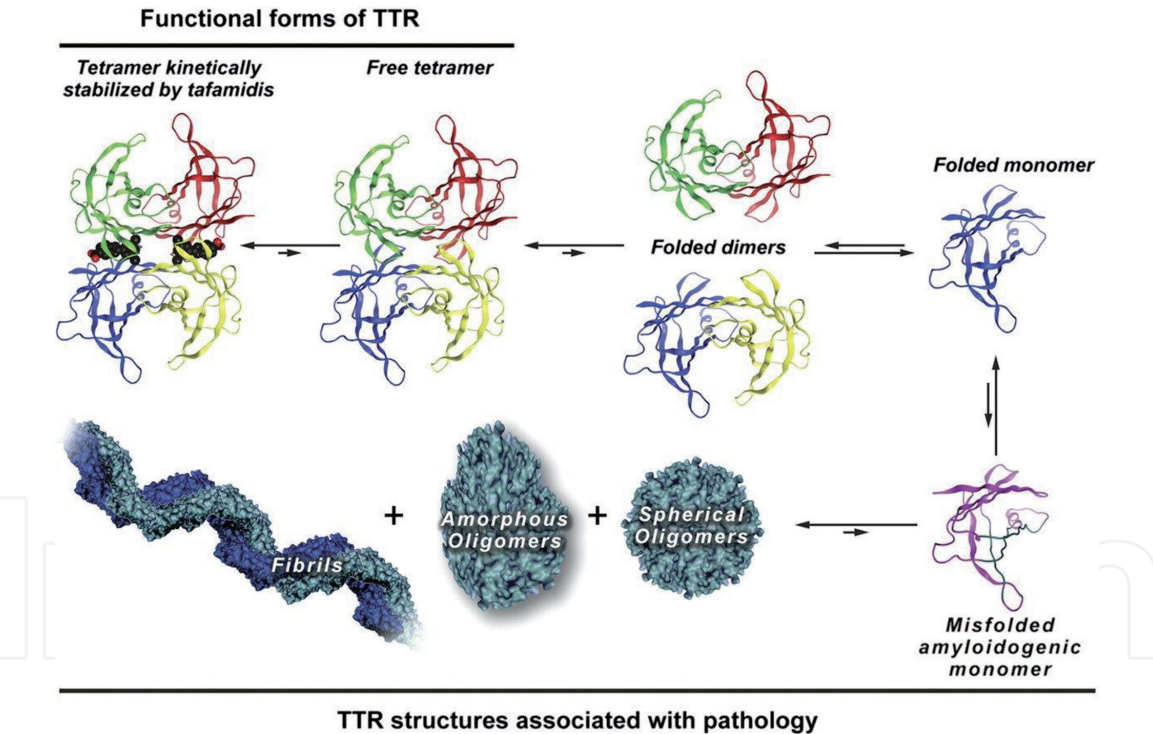
**Keywords:** TTR, ATTR, transthyretin amyloidosis, ATTRwt, tafamidis, diflunisal, inotersen, patisiran

## 1. Introduction

Systemic amyloidosis comprises a group of diseases characterized by deposition of misfolded proteins which express abnormal  $\beta$ -sheet conformation usually in the extracellular spaces in different tissues [1]. At least 36 amyloid precursor proteins are recognized so far in the humans [2]. There are several general pathogenetic pathways that proteins become misfolded and create amyloid fibrils [3]: (1) presence of abnormal protein such as amyloid light chain (AL) or those caused by a mutation (such as familial ATTR and amyloidosis related to gelsolin mutations), (2) prolonged exposure to a normal protein such as systemic reactive (AA) and dialysis related amyloidosis; and (3) age related amyloidosis such as senile systemic amyloidosis. This book chapter will discuss the neurological manifestations of familial and wild-type ATTR, their diagnosis and treatment. Although neuropathy related to familial ATTR is uncommon, it is underdiagnosed and causes profound disability and mortality, largely as a result of concomitant cardiomyopathy. Timely diagnosis and treatment improves the outcome as new disease modifying treatments have become available.

## 2. Transthyretin (TTR)

TTR is a 127 amino acid protein, is encoded by 7 kb of DNA spanning exons 1–4 of a single gene on chromosome 18 [4]. TTR is a carrier molecule of thyroxine and vitamin A. Serum TTR is synthesized and excreted by the liver as a tetrameric structure. Other sources of local TTR synthesis include epithelial cells of the choroid plexus and the retinal pigment epithelium. TTR is however dispensable for thyroid hormone homeostasis; TTR knockout mice are euthyroid and have a normal phenotype [5, 6]. The presence of point mutations in TTR results in destabilization of the tetramere, and dissociation into amyloidogenic monomers, which misfold and self-aggregate into insoluble amyloid fibrils (**Figure 1**). Two distinct types of amyloid fibrils have been described in TTR amyloid deposits: type A, consists of C-terminal TTR fragments and full-length TTR, and type B, which only consists of full-length TTR [7]. Type A fibrils often target the heart and type B fibrils occur predominantly with neurological symptoms [8]. Every organ of an individual patient contains the same (either type A or type B) fibrils, and the composition is unchanged over time. The presence of C-terminal TTR fragments has an impact on the affinity for various tracers used for intensity of tissue Congo red staining and of noninvasive imaging of amyloid depositions using 99 m-technetium-diphosphono-propanodicarboxylic acid scintigraphy [7].



**Figure 1.** Amyloid formation by TTR requires rate-limiting tetramer dissociation to a pair of folded dimers, which then quickly dissociate into folded monomers. Partial unfolding of the monomers yields the aggregation-prone amyloidogenic intermediate. The amyloidogenic intermediate can misassemble to form a variety of aggregate morphologies, including spherical oligomers, amorphous aggregates, and fibrils. Tafamidis binding to the TTR tetramer (upper left, see text below) dramatically slows dissociation, thereby efficiently inhibiting aggregation [from [63], with permission].

## 3. Familial transthyretin related amyloidosis (fATTR)

fATTR is a multisystem disease involving the heart (cardiomyopathy, conduction disturbances), gastrointestinal tract, kidneys, thyroid, salivary glands, eyes, peripheral and central nervous system. More than 130 pathological mutations have been associated with fATTR [9, 10].

### 3.1 Epidemiology

There is a marked variation in the prevalence and age of onset of ATTR in different countries, partly as a result of variation in the type of pathogenic mutation. ATTR is endemic in northern Portugal, Sweden and Japan, but sporadically occurs everywhere in the globe, with estimated number of about 5–10,000 patients worldwide [11]. The global prevalence is estimated at 0.87–1.1 per million; prevalence in Europe and Japan are estimated at 1/100,000 and 1 per million individuals respectively [12, 13]. The age of onset has a wide range, between 10s and 90s [10]. In Japan, the age of onset is bimodal, with early (30–40 year old) and late (60s) onset peaks [10]; on the other hand, the age of onset is more likely to be early (25–35 years old) in Portugal and late in Sweden [14, 15]. The most common mutation associated with familial amyloid polyneuropathy (FAP) is Val30Met mutation (replacement of valine with methionine at position 30), with endemic spots in northern Portugal (where its prevalence is estimated at 1/538), Sweden, Japan, and Brazil. On the other hand, the most common mutation in the US metropolitan areas is Val122Ile (isoleucine is substituted for valine at position 122); this mutation almost exclusively occurs in patients of African descent and has the allele prevalence of 0.0173; i.e. 3.43% of African Americans carry at least one copy of the mutant gene [16]. Val122Ile related ATTR generally has a cardiac phenotype. In the UK population the majority of patients have the T60A missense mutation where tyrosine is replaced by adenine at position 60. This has been traced to a single founder mutation from north-west Ireland [17].

### 3.2 Neurological manifestations

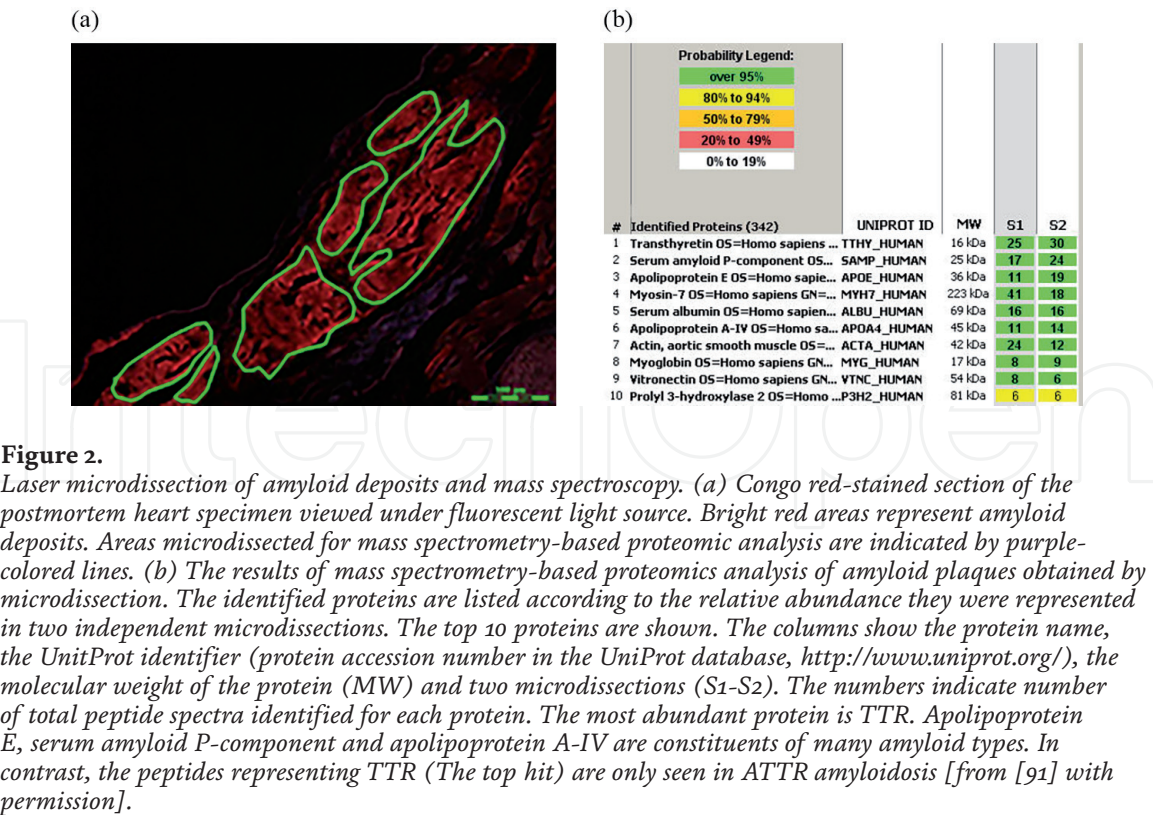
Depending on the mutation in TTR, the phenotype can be cardiologic, neurologic, or mixed. Neurological manifestations, particularly polyneuropathy are the most common manifestations of some of the mutations.

#### 3.2.1 Familial amyloid polyneuropathy (FAP)

FAP is the most common neurological manifestation of ATTR. It is autosomal dominant, but the penetrance is variable and dependent on the type of mutation. If untreated, patients will have progressive neuropathy and disability resulting in death 10–15 years after disease onset [18]. The Val30Met mutation is the most common mutation associated with FAP, with a variable disease phenotype. Early onset disease (age < 50), which is more common in endemic regions of Japan and Portugal has a high penetrance and presents with a progressive polyneuropathy predominantly involving the small fiber nerves, which is typically manifested by loss of distal pain and temperature sensation, and progressive autonomic dysfunction; the latter includes orthostatic hypotension, neurogenic bladder, erectile dysfunction and impaired bowel function (malabsorption, diarrhea and constipation), and the presence of cardiac conduction blocks often necessitate pacemaker placement [10, 19]. On the other hand, late onset (>50 year old) phenotype, which occurs in non-endemic regions of Portugal, Sweden and Japan and sporadic cases in other parts of the world, is characterized by a low penetrance rate, male sex predominance. Late onset cases may not have significant clinical dysautonomia, and often present with a progressive distal neuropathy involving large and small fiber modalities, presenting with motor weakness and loss of vibratory and position sense early on, often with significant neuropathic pain. Autonomic dysfunction was the initial manifestation of 48% of early onset and 10% of late onset FAP in a previous study [20]. Late onset FAP is often misdiagnosed for more common entities in that age group such as idiopathic neuropathy



or chronic inflammatory demyelinating polyneuropathy (CIDP) partly because of lack of positive family history and autonomic symptoms [9, 19, 21]. Other reasons for misdiagnosis include presence of demyelinating features in the nerve conduction study, elevated cerebrospinal fluid (CSF) protein level [22, 23], and negative abdominal fat pad or nerve biopsy for Congo-red amyloid staining [9]. In a previous study on patients with familial amyloid cardiomyopathy, abdominal fat pad and bone marrow biopsy showed amyloid deposits in 67 and 41% of the patients respectively, while a sural nerve biopsy was positive in 83% of the patients who had that procedure [27]. It is therefore very important to do an amyloidosis workup, including echocardiography, nuclear imaging studies, and nerve biopsy on CIDP patients who do not respond to immunomodulatory treatment [9, 22, 23]. Val122Ile is the most common fATTR mutation in the USA, and usually has a cardiac phenotype, rather similar to ATTRwt (see below) [24, 25]; but carpal tunnel syndrome is rather common and neuropathy has also been reported in Val122Ile ATTR [26]. Unusual neuropathy phenotypes of FAP include upper extremity onset, ataxic and motor predominant [13]. For example, FAP associated with T60A mutation (which is one of the more common mutations in UK) is characterized by a non-length dependent sensory loss and motor deficits, often rapidly progressive disease, and lack of positive sensory symptoms [17]. There is a diagnostic delay of up to 4 years for FAP diagnosis, especially when the autonomic symptoms are lacking [9, 21, 27]; As effective treatments are now available for FAP, it is very important to diagnose it in early stages, and before the cardiovascular and neurological disability are not severe. Presence of “red-flag” symptomatology have been emphasized to expedite the diagnosis, these include positive family history for neuropathy, unexplained heart disease including but not limited to atrial fibrillation, cardiac hypertrophy on echocardiography, carpal tunnel syndrome, gastrointestinal symptoms (anorexia, constipation, diarrhea, nausea, vomiting and unexplained weight loss, alternating constipation and diarrhea), renal involvement (proteinuria and renal failure) and ocular disease. The presence of >1 of the aforementioned features should prompt genetic testing for fATTR, as well as neurological and cardiovascular workup directed at the detection of amyloidosis [10, 28]. Gene sequencing has become increasingly affordable, and currently can be done free of charge for some patients in the USA ([www.invitae.com/en/alnylam-act-hattr-amyloidosis](http://www.invitae.com/en/alnylam-act-hattr-amyloidosis); [www.ambrygen.com/partners/hattr-compass/healthcare-provider](http://www.ambrygen.com/partners/hattr-compass/healthcare-provider)). Another rather common diagnostic challenge is differentiating ATTR from primary (AL) amyloidosis. Monoclonal gammopathy of unclear significance (MGUS) has been reported in ~20–50% of patients with ATTR cardiomyopathy [29, 30]. Very high (>5.0) or low (<0.2) kappa/lambda ratio usually imply AL amyloidosis whereas normal ratio (0.7–1.2) suggests ATTR [31]. Sometimes, however, the result of kappa/lambda ratio is inconclusive. Immunohistochemistry (IHC), i.e. staining of amyloid deposits with antibodies to kappa and lambda light chains as well as TTR can be used to make the differentiation between AL amyloidosis and ATTR, however, amyloid subtype cannot be determined in 20–25% of cases with IHC alone [32]. Laser capture microdissection of amyloid deposits (microdissection done on Congo red stained tissue materials) followed by mass spectrometry has increased the sensitivity and specificity of amyloid subtyping to 98–100% [32, 33] (**Figure 2**). Lipid chromatography-tandem mass spectrometry (LC-MS/MS) is another, more recent technology which determines the presence of mutant peptides with rather high accuracy [33–35]. However, LC-MS/MS had a sensitivity of 84% in picking up mutations that were detected in the genetic testing in a recent US study on 56 patients with fATTR cardiomyopathy [36]. Eight of the nine patients with mismatch between genetic testing and LC-MS/MS in the aforementioned study



were African Americans, two of whom were homozygote to Val122Ile mutation. Sensitivity of LC-MS/MS to pick up mutations is diminished in instances that mutation does not result in significant mass shift, or is located in regions of the gene with short tryptic peptides [34, 37]. Nuclear imaging studies, using bone avid tracers 99mTc-DPD (technetium-3,3-diphosphono-1,2-propanodicarboxylic acid), 99mTc-PYP (technetium-pyrophosphate) and 99mTc-HMDP (technetium-hydroxymethylene diphosphonate) have been increasingly used to diagnose ATTR related cardiomyopathy as they are widely available, have good sensitivity and are not costly [38, 39]. Demonstration of cardiac uptake using the aforementioned methods in a patient with neuropathy and heart disease strongly suggests ATTR if AL amyloidosis is excluded using serum and urine immunoelectrophoresis/immunofixation and assessment of serum free light chains [29].

### 3.2.2 Familial leptomeningeal and oculomeningeal amyloidosis

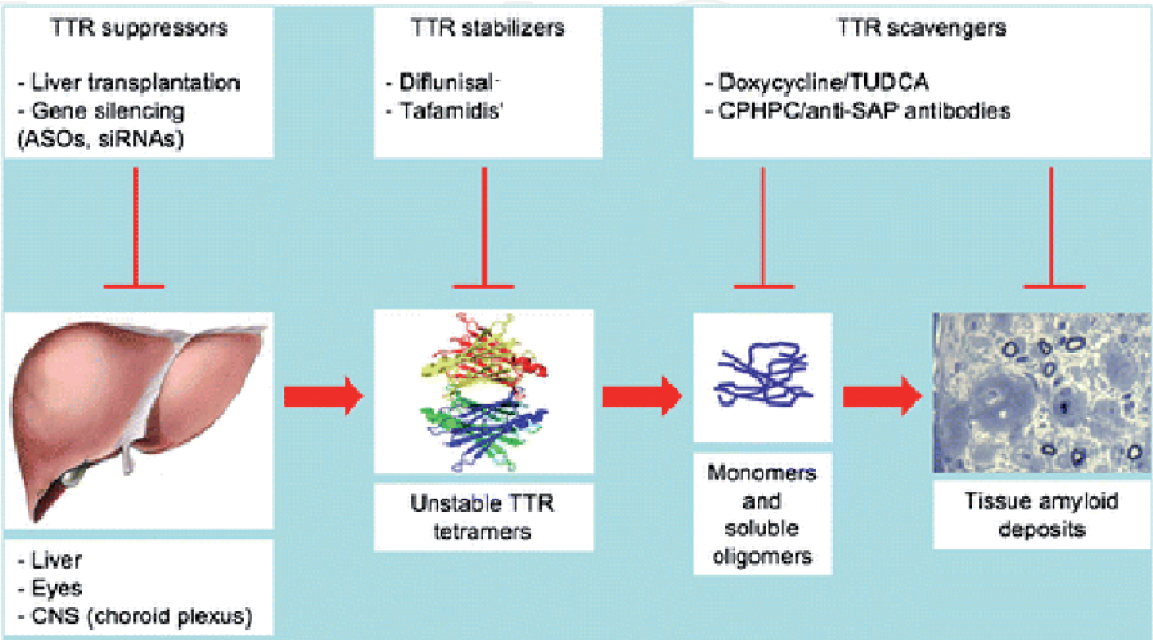
Leptomeningeal and meningovascular amyloidosis, often with concomitant vitreous opacity, are rare neurological manifestations of fATTR. Leptomeningeal amyloidosis has been reported with different TTR mutations (Val30Met, Val30Gly, Leu12Pro, Phe64Ser, Ala36Pro, Gly53Glu, Tyr69His, Ala25Thr, Tyr114Cys, Asp18Gly), sometimes in combination with FAP [40–47]. CNS symptoms include stroke, subarachnoid hemorrhage, dementia, hydrocephalus, ataxia, seizures, and sensorineural hearing loss. MRI studies may demonstrate leptomeningeal enhancement and superficial siderosis (sequela of intracranial bleedings) and there may be markedly elevated CSF protein [46, 48]. Ocular and meningovascular manifestations are specially common after liver transplantation, as the patient lives longer and mutant TTR is still being ecreted from the retinal cells and choroid plexus [49]. A previous study demonstrated that 27/87 (31%) of patients with Val30Met related FAP had focal neurological episodes, which occurred on average >14 years after the onset of FAP; more common after liver transplantation but also in patients with milder phenotypes which have a longer survival [47].

3.3 Treatment of familial ATTR

Disease modifying treatments have become available for FAP since 1990s, starting with liver transplantation (**Figure 3**). Treatment strategies include: (1), depleting the source of mutant TTR (liver transplantation); (2), inhibition of formation of TTR (wild type and mutant), by preventing translation of mRNA with antisense oligonucleotide (ASO) or with small interfering RNA (siRNA) technologies; (3), stabilization of TTR tetramere by small molecules (diflunisal and tafamidis); and (4), therapy directed to remove the amyloid deposits [19]. Currently approved disease modifying treatments by US food and drug administration (FDA) include inotersen and patisiran; with tafamidis approval under FDA review.

3.3.1 Liver transplantation

Removing the source of mutant TTR (liver) was the first disease modifying treatment for FAP. Liver transplantation, however, involves a major surgery, which is not tolerated with patients with significant underlying cardiovascular disease, and necessitates lifelong immunosuppression. Overall 5 year survival after liver transplantation is ~80% [50]. The 5 and 10 years survival rates post- transplantation were significantly better after Val30Met cases (82 and 74%) than the other mutations [50, 51]. Cardiomyopathy is a major determinant of prognosis with 10-year survival rates of 92 and 64% post-transplantation for patients without and with cardiomyopathy in a previous study [52]. Furthermore, liver transplant is more effective in changing the natural course of the disease in early onset Val30Met than the late onset cases, which could be due to more severe cardiomyopathy in the latter subtype [53]. Liver transplant is not an effective treatment for ATTRwt, leptomeningeal and ocular amyloidosis. Although ~90% of patients with early sensory neuropathy demonstrate disease stability after a liver transplant, organ involvement is not usually reversed, furthermore, FAP, and specially cardiomyopathy often deteriorate gradually post-transplant due to the deposition of ATTRwt [54, 55]. Advanced age and malnutrition are also risk factors for poor outcome/survival after liver transplantation [53, 56], partly because there is more predisposition to deposition of wild-type TTR in older age.



**Figure 3.**  
*Treatment strategies for fATTR (modified, from [92], with permission).*



Combined liver-kidney or liver-heart, and rarely liver-heart-kidney transplantation has been used for FAP patients with advanced renal or heart disease [55].

### 3.3.2 Stabilizers of TTR tetramere

Nonsteroidal anti-inflammatory drugs (NSAIDs) and tafamidis meglumine inhibit TTR tetramere degradation and therefore formation of amyloidogenic monomers. NSAIDs have structural resemblance to thyroxine, a natural tetramere stabilizer. Diflunisal and tafamidis are disease modifying treatments for fATTR.

#### 3.3.2.1 Diflunisal

In a randomized, double blinded, placebo controlled trial on 130 patients with FAP, diflunisal 250 mg twice a day was well tolerated and slowed the progression of neuropathy over a period of 2 years [57]. In that study, the Neuropathy Impairment +7 (NIS + 7) score increased by an average of 25.0 points in the placebo group versus 8.7 points in the diflunisal group (increase indicates deterioration of neuropathy). On the other hand, diflunisal also had a favorable effect on the quality of life; average of 36-Item Short-Form Health Survey (SF-36) physical scores decreased by 4.9 points in the placebo group and increased by 1.5 points in the diflunisal group. Modified body mass index (BMI), the product of serum albumin concentration (measured in grams per liter) and BMI (calculated as weight in kilograms divided by height in meters squared), which is an indicator of malnutrition and correlates with survival in FAP [58, 59], was the only endpoint which did not show improvement with diflunisal. In another study on 40 Japanese patients with fATTR, diflunisal was effective on neurological and cardiological manifestations after a period of 24 months, 3 patients could not tolerate diflunisal because of declining renal function or thrombocytopenia [60]. Diflunisal is inexpensive and widely available, but some of the potential problems associated with NSAIDs in general, such as gastrointestinal adverse effects including bleeding, limit its use, and caution is to be exercised in its use in the setting of underlying heart or kidney disease [61].

#### 3.3.2.2 Tafamidis (Vyndaqel)

Tafamidis was approved in European Union in 2011, for adult patients with early FAP regardless of the type of mutation [12]. It has since also been approved in Argentina, Japan and Mexico, for delaying the neurological disabilities of FAP [62]. Tafamidis binds selectively to the two normally unoccupied thyroxine-binding sites of the tetramer, and kinetically stabilizes TTR, including the less stable mutant TTR tetramers, preventing the tetramer dissociation, which is the rate-limiting step in the generation of amyloidogenic monomers [63] (**Figure 1**). In a previous study, 98% of the patients had TTR stabilization after 18 months of tafamidis [64]. Tafamidis is more effective in early onset Val30Met cases than late onset Val30Met and non-Val30Met mutations, there was progression of disability score in 55% and deterioration of neuropathy score of most of patients with late-onset ATTR V30 M involved in a nonrandomized controlled trial [13]. In a double blinded multicenter study, tafamidis 20 mg per day, was compared to placebo in an 18-month study in adult patients with early-stage Val30Met TTR-FAP [64]. There were no statistically significant differences between tafamidis and placebo for the coprimary endpoints (changes of the Neuropathy Impairment Score-Lower Limb (NIS-LL) and Norfolk Quality-of-Life (QOL) Diabetic-Neuropathy Questionnaire) in the intent to treat population, which included patients who dropped out for liver transplantation. On the other hand, in the efficacy evaluable



population, tafamidis patients had significantly better outcomes with the primary endpoints. Furthermore, tafamidis group had more favorable outcomes in the secondary endpoints which included changes in neurologic function, nutritional status, and TTR stabilization. Tafamidis is generally well tolerated including in long term, post-marketing, extension studies, with the majority of adverse effects of mild to moderate severity [64, 65].

### *3.3.3 Gene therapies*

Inhibiting the transcription of TTR mRNA by gene silencing technologies such as antisense oligonucleotides (ASO) and small interfering RNAs (siRNA) constitute most promising approaches in the treatment of FAP. Inotersen and patisiran were approved by FDA in 2018.

#### *3.3.3.1 Inotersen*

Inotersen is a 2'-O-methoxyethyl-modified ASO, which selectively binds to the TTR complementary RNA and inhibits the liver synthesis of both wild-type and mutant TTR. In a double blinded 15 months study, NEURO-TTR, FAP patients in earlier neuropathy stages (ambulatory with or without assistance) received weekly subcutaneous injections of inotersen 300 mg after loading dose of 3 doses in the first week, versus placebo [66]. All of the patients also received daily Vitamin A supplementation 3000 IU. The serum TTR level in the inotersen group significantly dropped from its baseline with a median nadir of 79.0% from week 13 to 65. Inotersen recipients did significantly better in the primary endpoints: there was a difference in the least-square mean of 19.7 points in modified Neuropathy Impairment Score+7 (mNIS+7) and 11.7 points in Norfolk Quality of Life-Diabetic Neuropathy (QOL-DN), favoring inotersen group, after 66 weeks of treatment. Inotersen also slowed the weight loss with a statistical trend towards efficacy on decline of BMI. Improvement of the course of FAP and quality of life in the patients who received inotersen occurred regardless of the mutation type or the presence of cardiomyopathy. This study did not have sufficient power to assess efficacy of inotersen on cardiomyopathy. Significant side effects of inotersen included glomerulonephritis and thrombocytopenia. 23% of inotersen recipients developed a platelet count below  $100 \times 10^9/L$ , and three patients had platelet counts to  $<25 \times 10^9/L$ , one of whom died of brain hemorrhage. Antiplatelet antibodies were positive in all of the 3 patients with severe thrombocytopenia pointing to the immune mediated nature of this complication. As thrombocytopenia associated with ASO treatment can be severe and fatal, platelet counts should be closely monitored in patients who receive inotersen. Patients who developed nephropathy had a crescentic glomerulonephritis on the background of amyloidosis, kidney function in one patients improved after treatment with prednisone and cyclophosphamide; therefore, monitoring of kidney function and urine protein are also necessary during treatment with inotersen. As a matter of fact, there was no additional cases of severe thrombocytopenia, and only a single patient developed a mild glomerulonephritis after the implementation of enhanced monitoring in the NEURO-TTR study. Local skin reactions were generally mild and did not result in discontinuation of the treatment in any patient.

#### *3.3.3.2 Patisiran*

Patisiran is a siRNA oligonucleotide wrapped in nanoparticles for specialized delivery to the liver, where it targets the 3' untranslated region of TTR's messenger RNA, resulting its cleavage, and therefore lack of transcription of TTR mRNA to

a protein product. Treatment with patisiran therefore results in reduction in the production of both wild-type and mutant TTR. After preliminary studies showed dose dependent reduction of serum TTR in normal subjects and patients with FAP who received patisiran, and possible favorable effect on the course of neuropathy in a phase 2 study [67, 68], a recent phase 3 double blinded (APOLLO) study compared patisiran 0.3 mg/kg every 3 weeks intravenously to placebo in patients with FAP [69]. Patients who had undergone liver transplantation or those with advanced heart failure were excluded. Treatment with patisiran resulted in sustained reduction of serum TTR over a period of 18 months (median 81%, range – 38–95). Patisiran recipients did significantly better in all primary endpoints: the least-squares mean mNIS+7 change from baseline was –6.0 in the patisiran versus + 28.0 in the placebo group (difference of 34.0 points favoring the patisiran group;  $P < 0.001$ ) and the effect could be seen as early as 9 months; The least-squares mean change from baseline in Norfolk QOL-DN was –6.7 in patisiran versus 14.4 in the placebo group (difference, –21.1 points,  $P < 0.001$ ); patisiran recipients also did better with the modified BMI and gait speed. Fifty one percent of patients who received patisiran versus 10% of those on placebo had improvement in the Norfolk QOL-DN score after 18 months. Treatment efficacy included patients with Val30Met as well as other mutations, and included sensory, motor and autonomic aspects of neuropathy. Patients in the patisiran group also had better cardiac outcomes, i.e. changes in NT-proBNP, left ventricular wall thickness and longitudinal stress, than those on placebo. The side effects that were more common in the patisiran than the placebo included infusion-related reactions (19%) and peripheral edema (30%). Infusion reactions (back pain, flushing, abdominal pain, and nausea) were mild to moderate and only one patient dropped from the study as their result. Thrombocytopenia and nephropathy were not among the patisiran related side effects in that study.

#### *3.3.4 Other potential treatments*

A combination of doxycycline, which is proposed to disrupt deposited fibrillar TTR amyloid fibrils [19, 55, 70] and tauroursodeoxycholic acid (a biliary acid, and also a disrupter of nonfibrillar TTR) has been effective in removal of amyloid deposits in a mouse model [71]. Another promising approach to resolve existing amyloid deposits is targeting serum amyloid P (SAP) component, which has an avid binding to all amyloid fibril types, resulting in stabilization of the amyloid fibrils and preventing their proteolysis [72]; antibodies to SAP have been promising in animal models of amyloidosis [73], and are being investigated in different forms of human amyloidosis.

## **4. Wild-type ATTR (ATTRwt), aka. senile systemic amyloidosis**

Systemic Deposition of ATTRwt is a rather common process associated with aging. Previous studies have reported a prevalence of 12–25% for tissue deposition of ATTRwt in people older than 80 year old [74, 75]. Despite very common prevalence in postmortem and tissue studies, ATTRwt is not a very recognized entity among the community physicians and therefore it is rather underdiagnosed. Patients with ATTRwt typically present with cardiac manifestations, including congestive heart failure, atrial fibrillation and other arrhythmias. ATTRwt is increasingly diagnosed as a cause of heart failure with preserved ejection fraction (HFpEF) [76]. Embolic events are frequently encountered, mean survival period from the onset of congestive heart failure symptoms is ~75 months [19]. There are differences between fATTR and ATTRwt in the pattern and shape of tissue amyloid

deposition [74]. In fATTR deposits are predominantly localized in the pericardium and surrounding muscle fascicles, on the other hand, they have patchy plaque-like shapes and mostly appear inside the ventricular wall in ATTRwt cases. Differences also exist between the shape of deposited amyloid fibrils between fATTR and ATTRwt in electron microscopy: in fATTR, long, straight fibrils are arranged in parallel, whereas short, rigid fibrils with haphazard arrangement are noted in ATTRwt, with endocardial region more involved than epicardium [74]. ATTRwt also involves other organs, often subclinically. In the pathological study by Ueda, et al., amyloid deposits were noted in bladder in 5/6 cases; deposits in the thyroid, pancreas, liver, gallbladder, adrenal gland, and gastrointestinal tract were mainly located in the walls of small arteries [74].

#### **4.1 Diagnosis of ATTRwt**

It should be noted that significant amount of ATTRwt deposition, not a mere presence, is needed to establish a pathogenic role [77]. ATTRwt is most commonly diagnosed in the setting of a late onset cardiomyopathy. Tissue deposition of amyloid with Congo Red staining and subsequent immunohistochemical or proteomic analysis of the amyloid deposits along with a TTR gene sequencing (which does not show a pathogenic Mutation) are usually needed to diagnose ATTRwt. On the other hand, Technetium-labeled bone scintigraphy tracers are long to be known to be able to detect myocardial amyloid deposits, and use of this imaging modality for the diagnosis of cardiac ATTR amyloidosis has been increasingly. In a recent study on 857 patients with histologically proven cardiac amyloid (374 with endomyocardial biopsies) and 360 patients with nonamyloid cardiomyopathies, myocardial radiotracer uptake on bone scintigraphy was >99% sensitive and 86% specific for cardiac ATTR amyloid, with false positives exclusively due to cases with AL amyloidosis [29]. Therefore cardiac ATTR can be diagnosed without a tissue biopsy and exclusion of AL amyloidosis based on serum and urine immunofixation and free lambda and kappa levels. Similar to the situation with fATTR, high prevalence of MGUS in ATTRwt poses a diagnostic challenge. About one fourth to 50% of patients with ATTRwt have a monoclonal gammopathy in the serum or urine and ~10% have a high serum kappa/lambda ratio [30, 78, 79]. It should be noted that abdominal fat pad aspiration and biopsy have a low sensitivity for ATTRwt, 12–14% on some of the previous studies [80, 81], although using abdominal fat pad biopsy, sensitivity of 73% has also been reported in another study [82].

#### **4.2 Neurological manifestations of ATTRwt**

ATTRwt is generally not associated with a polyneuropathy. A previous report suggested ATTRwt as a cause of a rapidly progressive neuropathy in an elderly woman; amyloid deposits were present in the gastrocnemius, but not the sural nerve of that patient [83]. On the other hand, ATTRwt is rather commonly associated with late onset musculoskeletal problems, particularly carpal tunnel syndrome and lumbar spinal stenosis, but overall it is underdiagnosed. ATTRwt deposits have been demonstrated in about one third of tenosynovial tissues obtained during carpal tunnel release operation in elderly patients [84, 85], as well as in 30–45% of the resected tissues harvested during decompression surgeries for lumbar spinal stenosis [77, 86].

The ATTRwt deposits are frequently minimal and may not be important from the pathogenesis standpoint [77]. On the other hand, more prominent amyloid



deposition may play a role in spinal stenosis as they cause increased thickness of ligamentum flavum or abnormal spinal stability [86]. Examination of tenosynovial tissue on 100 patients with idiopathic CTS showed positive Congo Red staining on 34 patients, all also positively staining with anti TTR antibody with negative gene sequencing, consistent with ATTRwt [84]. On the other hand, in a single center study involving 31 ATTRwt patients, CTS was the most common presenting symptom in more than 50% of the patients [87]. In another recent prospective study on 98 patients with idiopathic CTS in men >60 year and women >50, who underwent decompressive surgery, amyloid deposits were found in 10 patients, 5 of which turned out to be due to ATTRwt [88]. Spinal cord compression secondary to ATTRwt has also been rarely reported [89, 90]. Myopathy is rarely reported as a feature of ATTRwt, but in the author's opinion it is underdiagnosed. We previously reported a patient who presented with bent spine syndrome due to ATTRwt related myopathy affecting the thoracic paraspinal muscles [91]. That patient succumbed as the result of consequences of cardiomyopathy and a cardio-embolic stroke.

### **4.3 Treatment of ATTRwt**

Although TTR stabilizers and suppressors of gene expression will likely suppress ATTRwt deposition, there are no current FDA approved disease modifying therapies for ATTRwt and the management remains to be symptomatic, such as medical treatment of heart failure and arrhythmias, including insertion of defibrillator/pacemaker, and heart transplantation if necessary. Treatment of neuromuscular complications remains to be symptomatic as well, i.e. decompression surgeries of myelopathy and lumbar spinal stenosis and carpal tunnel syndrome release. The reasons for lack of disease modifying treatments include the fact that ATTRwt is underdiagnosed and the natural history of its neuromuscular complications is unknown. Furthermore, ATTRwt is a disease of older population and neuromuscular complications are likely overshadowed by other medical comorbidities specially heart disease [78], and therefore the effect of disease modifying treatments would be difficult to assess.

## **5. Conclusions**

Familial amyloid polyneuropathy is a rare, but treatable cause of neuropathy, diagnosis in an early stage is essential to establish disease modifying treatment at a stage which the disability can be prevented from progression or potentially reversed. Diagnosis should be suspected when red-flag symptomatology is present in a patient with neuropathy; and can possibly be established by sequencing of transthyretin gene. Musculoskeletal disease such as carpal tunnel syndrome and spinal stenosis are early manifestations and underdiagnosed causes of wild-type transthyretin amyloidosis. Increased cardiac uptake on nuclear imaging studies is a sensitive, widely available diagnostic modality for early diagnosis of familial and wild-type transthyretin amyloidosis.

### **Conflict of interest**

Dr. Rezania has received funding from Amyotrophic Lateral Sclerosis Association (ALSA) and National Institute of Neurological Disorders and Stroke; has served on the advisory boards of Alnylam, Alexion and MT Pharma; has received honoraria for

giving speeches from Alexion, MT Pharma Tanabe, Kabafusion, Option Care, Sanofi-Genzyme, and American Association of Neuromuscular and Electrodiagnostic Medicine; has received royalties from Medlink.

Acronyms and abbreviations

TTR	transthyretin
ATTR	transthyretin related amyloidosis
fATTR	familial transthyretin related amyloidosis
ATTRwt	wild-type transthyretin related amyloidosis
CIDP	chronic inflammatory demyelinating polyneuropathy
FAP	familial amyloid polyneuropathy

Author details

Kourosh Rezaia<sup>1\*</sup> and Laleh Saadat<sup>2</sup>

1 Department of Neurology, University of Chicago Medical Center, Chicago, IL, USA

2 Department of Surgery, University of Chicago Medical Center, Chicago, IL, USA

\*Address all correspondence to: krezania@neurology.bsd.uchicago.edu

IntechOpen

© 2019 The Author(s). Licensee IntechOpen. This chapter is distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/3.0>), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited. 

## References

- [1] Lachmann HJ, Hawkins PN. Systemic amyloidosis. *Current Opinion in Pharmacology*. 2006;**6**(2):214-220
- [2] Sipe JD, Benson MD, Buxbaum JN, Ikeda SI, Merlini G, Saraiva MJ, et al. Amyloid fibril proteins and amyloidosis: Chemical identification and clinical classification International Society of Amyloidosis 2016 Nomenclature Guidelines. *Amyloid*. 2016;**23**(4):209-213
- [3] Wechalekar AD, Gillmore JD, Hawkins PN. Systemic amyloidosis. *Lancet*. 2016;**387**(10038):2641-2654
- [4] Wallace MR, Naylor SL, Kluge-Beckerman B, Long GL, McDonald L, Shows TB, et al. Localization of the human prealbumin gene to chromosome 18. *Biochemical and Biophysical Research Communications*. 1985;**129**(3):753-758
- [5] Episkopou V, Maeda S, Nishiguchi S, Shimada K, Gaitanaris GA, Gottesman ME, et al. Disruption of the transthyretin gene results in mice with depressed levels of plasma retinol and thyroid hormone. *Proceedings of the National Academy of Sciences of the United States of America*. 1993;**90**(6):2375-2379
- [6] Palha JA. Transthyretin as a thyroid hormone carrier: Function revisited. *Clinical Chemistry and Laboratory Medicine*. 2002;**40**(12):1292-1300
- [7] Suhr OB, Lundgren E, Westermarck P. One mutation, two distinct disease variants: Unravelling the impact of transthyretin amyloid fibril composition. *Journal of Internal Medicine*. 2017;**281**(4):337-347
- [8] Fandrich M, Nystrom S, Nilsson KPR, Bockmann A, LeVine H, 3rd, Hammarstrom P. Amyloid fibril polymorphism: A challenge for molecular imaging and therapy. *Journal of Internal Medicine*. 2018;**283**(3):218-237
- [9] Plante-Bordeneuve V, Ferreira A, Lalu T, Zaros C, Lacroix C, Adams D, et al. Diagnostic pitfalls in sporadic transthyretin familial amyloid polyneuropathy (TTR-FAP). *Neurology*. 2007;**69**(7):693-698
- [10] Sekijima Y, Ueda M, Koike H, Misawa S, Ishii T, Ando Y. Diagnosis and management of transthyretin familial amyloid polyneuropathy in Japan: Red-flag symptom clusters and treatment algorithm. *Orphanet Journal of Rare Diseases*. 2018;**13**(1):6
- [11] Schmidt HH, Waddington-Cruz M, Botteman MF, Carter JA, Chopra AS, Hopps M, et al. Estimating the global prevalence of transthyretin familial amyloid polyneuropathy. *Muscle & Nerve*. 2018;**57**(5):829-837
- [12] Ando Y, Coelho T, Berk JL, Cruz MW, Ericzon BG, Ikeda S, et al. Guideline of transthyretin-related hereditary amyloidosis for clinicians. *Orphanet Journal of Rare Diseases*. 2013;**8**:31
- [13] Adams D, Theaudin M, Cauquil C, Algalarrondo V, Slama M. FAP neuropathy and emerging treatments. *Current Neurology and Neuroscience Reports*. 2014;**14**(3):435
- [14] Holmgren G, Costa PM, Andersson C, Asplund K, Steen L, Beckman L, et al. Geographical distribution of TTR met30 carriers in northern Sweden: Discrepancy between carrier frequency and prevalence rate. *Journal of Medical Genetics*. 1994;**31**(5):351-354
- [15] Sousa A, Coelho T, Barros J, Sequeiros J. Genetic epidemiology of familial amyloidotic polyneuropathy (FAP)-type I in Povoá do Varzim and



- Vila do Conde (north of Portugal). *American Journal of Medical Genetics*. 1995;**60**(6):512-521
- [16] Jacobson DR, Alexander AA, Tagoe C, Buxbaum JN. Prevalence of the amyloidogenic transthyretin (TTR) V122I allele in 14 333 African-Americans. *Amyloid*. 2015;**22**(3):171-174
- [17] Carr AS, Pelayo-Negro AL, Evans MR, Laura M, Blake J, Stancanelli C, et al. A study of the neuropathy associated with transthyretin amyloidosis (ATTR) in the UK. *Journal of Neurology, Neurosurgery, and Psychiatry*. 2016;**87**(6):620-627
- [18] Plante-Bordeneuve V, Lalu T, Misrahi M, Reilly MM, Adams D, Lacroix C, et al. Genotypic-phenotypic variations in a series of 65 patients with familial amyloid polyneuropathy. *Neurology*. 1998;**51**(3):708-714
- [19] Sekijima Y. Transthyretin (ATTR) amyloidosis: Clinical spectrum, molecular pathogenesis and disease-modifying treatments. *Journal of Neurology, Neurosurgery, and Psychiatry*. 2015;**86**(9):1036-1043
- [20] Koike H, Misu K, Ikeda S, Ando Y, Nakazato M, Ando E, et al. Type I (transthyretin Met30) familial amyloid polyneuropathy in Japan: Early- vs late-onset form. *Archives of Neurology*. 2002;**59**(11):1771-1776
- [21] Koike H, Tanaka F, Hashimoto R, Tomita M, Kawagashira Y, Iijima M, et al. Natural history of transthyretin Val30Met familial amyloid polyneuropathy: Analysis of late-onset cases from non-endemic areas. *Journal of Neurology, Neurosurgery, and Psychiatry*. 2012;**83**(2):152-158
- [22] Cappellari M, Cavallaro T, Ferrarini M, Cabrini I, Taioli F, Ferrari S, et al. Variable presentations of TTR-related familial amyloid polyneuropathy in seventeen patients. *Journal of the Peripheral Nervous System*. 2011;**16**(2):119-129
- [23] Mathis S, Magy L, Diallo L, Boukhris S, Vallat JM. Amyloid neuropathy mimicking chronic inflammatory demyelinating polyneuropathy. *Muscle & Nerve*. 2012;**45**(1):26-31
- [24] Buxbaum JN, Ruberg FL. Transthyretin V122I (pV142I)\* cardiac amyloidosis: An age-dependent autosomal dominant cardiomyopathy too common to be overlooked as a cause of significant heart disease in elderly African Americans. *Genetics in Medicine*. 2017;**19**(7):733-742
- [25] Quarta CC, Buxbaum JN, Shah AM, Falk RH, Claggett B, Kitzman DW, et al. The amyloidogenic V122I transthyretin variant in elderly black Americans. *The New England Journal of Medicine*. 2015;**372**(1):21-29
- [26] Carr AS, Pelayo-Negro AL, Jaunmuktane Z, Scalco RS, Hutt D, Evans MR, et al. Transthyretin V122I amyloidosis with clinical and histological evidence of amyloid neuropathy and myopathy. *Neuromuscular Disorders*. 2015;**25**(6):511-515
- [27] Wang AK, Fealey RD, Gehrking TL, Low PA. Patterns of neuropathy and autonomic failure in patients with amyloidosis. *Mayo Clinic Proceedings*. 2008;**83**(11):1226-1230
- [28] Conceicao I, Gonzalez-Duarte A, Obici L, Schmidt HH, Simoneau D, Ong ML, et al. "Red-flag" symptom clusters in transthyretin familial amyloid polyneuropathy. *Journal of the Peripheral Nervous System*. 2016;**21**(1):5-9
- [29] Gillmore JD, Maurer MS, Falk RH, Merlini G, Damy T, Dispenzieri A, et al. Nonbiopsy diagnosis of cardiac

transthyretin amyloidosis. *Circulation*. 2016;**133**(24):2404-2412

[30] Phull P, Sanchorawala V, Connors LH, Doros G, Ruberg FL, Berk JL, et al. Monoclonal gammopathy of undetermined significance in systemic transthyretin amyloidosis (ATTR). *Amyloid*. 2018;**25**(1):62-67

[31] Halushka MK, Eng G, Collins AB, Judge DP, Semigran MJ, Stone JR. Optimization of serum immunoglobulin free light Chain analysis for subclassification of cardiac amyloidosis. *Journal of Cardiovascular Translational Research*. 2015;**8**(4):264-268

[32] Gilbertson JA, Theis JD, Vrana JA, Lachmann H, Wechalekar A, Whelan C, et al. A comparison of immunohistochemistry and mass spectrometry for determining the amyloid fibril protein from formalin-fixed biopsy tissue. *Journal of Clinical Pathology*. 2015;**68**(4):314-317

[33] Vrana JA, Gamez JD, Madden BJ, Theis JD, Bergen HR, 3rd, Dogan A. Classification of amyloidosis by laser microdissection and mass spectrometry-based proteomic analysis in clinical biopsy specimens. *Blood*. 2009;**114**(24):4957-4959

[34] Dasari S, Theis JD, Vrana JA, Zenka RM, Zimmermann MT, Kocher JP, et al. Clinical proteome informatics workbench detects pathogenic mutations in hereditary amyloidoses. *Journal of Proteome Research*. 2014;**13**(5):2352-2358

[35] Klein CJ, Vrana JA, Theis JD, Dyck PJ, Dyck PJ, Spinner RJ, et al. Mass spectrometric-based proteomic analysis of amyloid neuropathy type in nerve tissue. *Archives of Neurology*. 2011;**68**(2):195-199

[36] Brown EE, Lee YZJ, Halushka MK, Steenbergen C, Johnson NM, Almansa J,

et al. Genetic testing improves identification of transthyretin amyloid (ATTR) subtype in cardiac amyloidosis. *Amyloid*. 2017;**24**(2):92-95

[37] Vrana JA, Theis JD, Dasari S, Mereuta OM, Dispenzieri A, Zeldenrust SR, et al. Clinical diagnosis and typing of systemic amyloidosis in subcutaneous fat aspirates by mass spectrometry-based proteomics. *Haematologica*. 2014;**99**(7):1239-1247

[38] Rapezzi C, Quarta CC, Guidalotti PL, Pettinato C, Fanti S, Leone O, et al. Role of (99m)Tc-DPD scintigraphy in diagnosis and prognosis of hereditary transthyretin-related cardiac amyloidosis. *JACC: Cardiovascular Imaging*. 2011;**4**(6):659-670

[39] Bokhari S, Castano A, Pozniakoff T, Deslisle S, Latif F, Maurer MS. (99m)Tc-pyrophosphate scintigraphy for differentiating light-chain cardiac amyloidosis from the transthyretin-related familial and senile cardiac amyloidoses. *Circulation. Cardiovascular Imaging*. 2013;**6**(2):195-201

[40] Herrick MK, DeBruyne K, Horoupian DS, Skare J, Vanefsky MA, Ong T. Massive leptomeningeal amyloidosis associated with a Val30Met transthyretin gene. *Neurology*. 1996;**47**(4):988-992

[41] Garzuly F, Vidal R, Wisniewski T, Brittig F, Budka H. Familial meningocerebrovascular amyloidosis, Hungarian type, with mutant transthyretin (TTR Asp18Gly). *Neurology*. 1996;**47**(6):1562-1567

[42] Petersen RB, Goren H, Cohen M, Richardson SL, Tresser N, Lynn A, et al. Transthyretin amyloidosis: A new mutation associated with dementia. *Annals of Neurology*. 1997;**41**(3):307-313

[43] Uemichi T, Uitti RJ, Koeppen AH, Donat JR, Benson

MD. Oculoleptomeningeal amyloidosis associated with a new transthyretin variant Ser64. *Archives of Neurology*. 1999;**56**(9):1152-1155

[44] Mascalchi M, Salvi F, Pirini MG, D'Errico A, Ferlini A, Lolli F, et al. Transthyretin amyloidosis and superficial siderosis of the CNS. *Neurology*. 1999;**53**(7):1498-1503

[45] Ellie E, Camou F, Vital A, Rummens C, Grateau G, Delpech M, et al. Recurrent subarachnoid hemorrhage associated with a new transthyretin variant (Gly53Glu). *Neurology*. 2001;**57**(1):135-137

[46] Jin K, Sato S, Takahashi T, Nakazaki H, Date Y, Nakazato M, et al. Familial leptomeningeal amyloidosis with a transthyretin variant Asp18Gly representing repeated subarachnoid haemorrhages with superficial siderosis. *Journal of Neurology, Neurosurgery, and Psychiatry*. 2004;**75**(10):1463-1466

[47] Maia LF, Magalhaes R, Freitas J, Taipa R, Pires MM, Osorio H, et al. CNS involvement in V30M transthyretin amyloidosis: Clinical, neuropathological and biochemical findings. *Journal of Neurology, Neurosurgery, and Psychiatry*. 2015;**86**(2):159-167

[48] Horowitz S, Thomas C, Gruener G, Nand S, Shea JF. MR of leptomeningeal spinal and posterior fossa amyloid. *AJNR. American Journal of Neuroradiology*. 1998;**19**(5):900-902

[49] Sekijima Y. Transthyretin-type cerebral amyloid angiopathy: A serious complication in post-transplant patients with familial amyloid polyneuropathy. *Journal of Neurology, Neurosurgery, and Psychiatry*. 2015;**86**(2):124

[50] 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

[51] Herlenius G, Wilczek HE, Larsson M, Ericzon BG. Familial Amyloidotic Polyneuropathy World Transplant R. Ten years of international experience with liver transplantation for familial amyloidotic polyneuropathy: Results from the Familial Amyloidotic Polyneuropathy World Transplant Registry. *Transplantation*. 2004;**77**(1):64-71

[52] Okamoto S, Wixner J, Ericzon BG, Friman S, Lindqvist P, Henein M, et al. Prognostic value of pre-transplant cardiomyopathy in Swedish liver transplanted patients for familial amyloidotic polyneuropathy. *Amyloid*. 2011;**18**(Suppl 1):171-173

[53] Okamoto S, Wixner J, Obayashi K, Ando Y, Ericzon BG, Friman S, et al. Liver transplantation for familial amyloidotic polyneuropathy: Impact on Swedish patients' survival. *Liver Transplantation*. 2009;**15**(10):1229-1235

[54] Yazaki M, Tokuda T, Nakamura A, Higashikata T, Koyama J, Higuchi K, et al. Cardiac amyloid in patients with familial amyloid polyneuropathy consists of abundant wild-type transthyretin. *Biochemical and Biophysical Research Communications*. 2000;**274**(3):702-706

[55] Carvalho A, Rocha A, Lobato L. Liver transplantation in transthyretin amyloidosis: Issues and challenges. *Liver Transplantation*. 2015;**21**(3):282-292

[56] Suhr OB, Ericzon BG, Friman S. Long-term follow-up of survival of liver transplant recipients with familial amyloid polyneuropathy (Portuguese type). *Liver Transplantation*. 2002;**8**(9):787-794

[57] Berk JL, Suhr OB, Obici L, Sekijima Y, Zeldenrust SR, Yamashita T, et al. Repurposing diflunisal for familial amyloid polyneuropathy: A randomized clinical trial. *Journal of the American Medical Association*. 2013;**310**(24):2658-2667



- [58] Suhr O, Danielsson A, Holmgren G, Steen L. Malnutrition and gastrointestinal dysfunction as prognostic factors for survival in familial amyloidotic polyneuropathy. *Journal of Internal Medicine*. 1994;**235**(5):479-485
- [59] Suhr OB, Holmgren G, Steen L, Wikstrom L, Norden G, Friman S, et al. Liver transplantation in familial amyloidotic polyneuropathy. Follow-up of the first 20 Swedish patients. *Transplantation*. 1995;**60**(9):933-938
- [60] 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**(2):79-83
- [61] Harirforoosh S, Asghar W, Jamali F. Adverse effects of nonsteroidal antiinflammatory drugs: An update of gastrointestinal, cardiovascular and renal complications. *Journal of Pharmacy & Pharmaceutical Sciences*. 2013;**16**(5):821-847
- [62] Scott LJ. Tafamidis: A review of its use in familial amyloid polyneuropathy. *Drugs*. 2014;**74**(12):1371-1378
- [63] Bulawa CE, Connelly S, Devit M, Wang L, Weigel C, Fleming JA, et al. Tafamidis, a potent and selective transthyretin kinetic stabilizer that inhibits the amyloid cascade. *Proceedings of the National Academy of Sciences of the United States of America*. 2012;**109**(24):9629-9634
- [64] Coelho T, Maia LF, Martins da Silva A, Waddington Cruz M, Plante-Bordeneuve V, Lozeron P, et al. Tafamidis for transthyretin familial amyloid polyneuropathy: A randomized, controlled trial. *Neurology*. 2012;**79**(8):785-792
- [65] Coelho T, Maia LF, da Silva AM, Cruz MW, Plante-Bordeneuve V, Suhr OB, et al. Long-term effects of tafamidis for the treatment of transthyretin familial amyloid polyneuropathy. *Journal of Neurology*. 2013;**260**(11):2802-2814
- [66] Benson MD, Waddington-Cruz M, Berk JL, Polydefkis M, Dyck PJ, Wang AK, et al. Inotersen Treatment for Patients with Hereditary Transthyretin Amyloidosis. *The New England Journal of Medicine*. 2018;**379**(1):22-31
- [67] Coelho T, Adams D, Silva A, Lozeron P, Hawkins PN, Mant T, et al. Safety and efficacy of RNAi therapy for transthyretin amyloidosis. *The New England Journal of Medicine*. 2013;**369**(9):819-829
- [68] Suhr OB, Coelho T, Buades J, Pouget J, Conceicao I, Berk J, et al. Efficacy and safety of patisiran for familial amyloidotic polyneuropathy: A phase II multi-dose study. *Orphanet Journal of Rare Diseases*. 2015;**10**:109
- [69] Adams D, Gonzalez-Duarte A, O'Riordan WD, Yang CC, Ueda M, Kristen AV, et al. Patisiran, an RNAi Therapeutic, for Hereditary Transthyretin Amyloidosis. *The New England Journal of Medicine*. 2018;**379**(1):11-21
- [70] Cardoso I, Saraiva MJ. Doxycycline disrupts transthyretin amyloid: Evidence from studies in a FAP transgenic mice model. *The FASEB Journal*. 2006;**20**(2):234-239
- [71] 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. *Journal of Translational Medicine*. 2010;**8**:74
- [72] Pepys MB, Dyck RF, de Beer FC, Skinner M, Cohen AS. Binding of serum amyloid P-component (SAP) by amyloid fibrils. *Clinical and Experimental Immunology*. 1979;**38**(2):284-293

- [73] Bodin K, Ellmerich S, Kahan MC, Tennent GA, Loesch A, Gilbertson JA, et al. Antibodies to human serum amyloid P component eliminate visceral amyloid deposits. *Nature*. 2010;**468**(7320):93-97
- [74] Ueda M, Horibata Y, Shono M, Misumi Y, Oshima T, Su Y, et al. Clinicopathological features of senile systemic amyloidosis: An ante- and post-mortem study. *Modern Pathology*. 2011;**24**(12):1533-1544
- [75] Tanskanen M, Peuralinna T, Polvikoski T, Notkola IL, Sulkava R, Hardy J, et al. Senile systemic amyloidosis affects 25% of the very aged and associates with genetic variation in alpha2-macroglobulin and tau: A population-based autopsy study. *Annals of Medicine*. 2008;**40**(3):232-239
- [76] Ton VK, Bhonsale A, Gilotra NA, Halushka MK, Steenbergen C, Almansa J, et al. Baseline characteristics predict the presence of amyloid on endomyocardial biopsy. *Journal of Cardiac Failure*. 2017;**23**(4):340-344
- [77] Westermark P, Westermark GT, Suhr OB, Berg S. Transthyretin-derived amyloidosis: Probably a common cause of lumbar spinal stenosis. *Upsala Journal of Medical Sciences*. 2014;**119**(3):223-228
- [78] Pinney JH, Whelan CJ, Petrie A, Dungu J, Banypersad SM, Sattianayagam P, et al. Senile systemic amyloidosis: Clinical features at presentation and outcome. *Journal of the American Heart Association*. 2013;**2**(2):e000098
- [79] Geller HI, Singh A, Mirto TM, Padera R, Mitchell R, Laubach JP, et al. Prevalence of monoclonal gammopathy in wild-type transthyretin amyloidosis. *Mayo Clinic Proceedings*. 2017;**92**(12):1800-1805
- [80] Fine NM, Arruda-Olson AM, Dispenzieri A, Zeldenrust SR, Gertz MA, Kyle RA, et al. Yield of noncardiac biopsy for the diagnosis of transthyretin cardiac amyloidosis. *The American Journal of Cardiology*. 2014;**113**(10):1723-1727
- [81] Garcia Y, Collins AB, Stone JR. Abdominal fat pad excisional biopsy for the diagnosis and typing of systemic amyloidosis. *Human Pathology*. 2018;**72**:71-79
- [82] Ikeda S, Sekijima Y, Tojo K, Koyama J. Diagnostic value of abdominal wall fat pad biopsy in senile systemic amyloidosis. *Amyloid*. 2011;**18**(4):211-215
- [83] Lam L, Margeta M, Layzer R. Amyloid polyneuropathy caused by wild-type transthyretin. *Muscle & Nerve*. 2015;**52**(1):146-149
- [84] Sekijima Y, Uchiyama S, Tojo K, Sano K, Shimizu Y, Imaeda T, et al. High prevalence of wild-type transthyretin deposition in patients with idiopathic carpal tunnel syndrome: A common cause of carpal tunnel syndrome in the elderly. *Human Pathology*. 2011;**42**(11):1785-1791
- [85] Gioeva Z, Urban P, Meliss RR, Haag J, Axmann HD, Siebert F, et al. ATTR amyloid in the carpal tunnel ligament is frequently of wildtype transthyretin origin. *Amyloid*. 2013;**20**(1):1-6
- [86] Yanagisawa A, Ueda M, Sueyoshi T, Okada T, Fujimoto T, Ogi Y, et al. Amyloid deposits derived from transthyretin in the ligamentum flavum as related to lumbar spinal canal stenosis. *Modern Pathology*. 2015;**28**(2):201-207
- [87] Nakagawa M, Sekijima Y, Yazaki M, Tojo K, Yoshinaga T, Doden T, et al. Carpal tunnel syndrome: A common initial symptom of systemic wild-type ATTR (ATTRwt) amyloidosis. *Amyloid*. 2016;**23**(1):58-63

[88] Sperry BW, Reyes BA, Ikram A, Donnelly JP, Phelan D, Jaber WA, et al. Tenosynovial and cardiac amyloidosis in patients undergoing carpal tunnel release. *Journal of the American College of Cardiology*. 2018;72(17):2040-2050

[89] Sueyoshi T, Ueda M, Sei A, Misumi Y, Oshima T, Yamashita T, et al. Spinal multifocal amyloidosis derived from wild-type transthyretin. *Amyloid*. 2011;18(3):165-168

[90] Rezaia K, Pytel P, Highsmith WE, Gabikian P. Cervicomedullary compression as the main manifestation of wild-type transthyretin amyloidosis. *Amyloid*. 2017;24(2):133-134

[91] Rezaia K, Pytel P, Smit LJ, Mastrianni J, Dina MA, Highsmith WE, et al. Systemic transthyretin amyloidosis in a patient with bent spine syndrome. *Amyloid*. 2013;20(2):131-134

[92] Kerschen P, Plante-Bordeneuve V. Current and future treatment approaches in transthyretin familial amyloid polyneuropathy. *Current Treatment Options in Neurology*. 2016;18(12):53