Chapter

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 β-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].

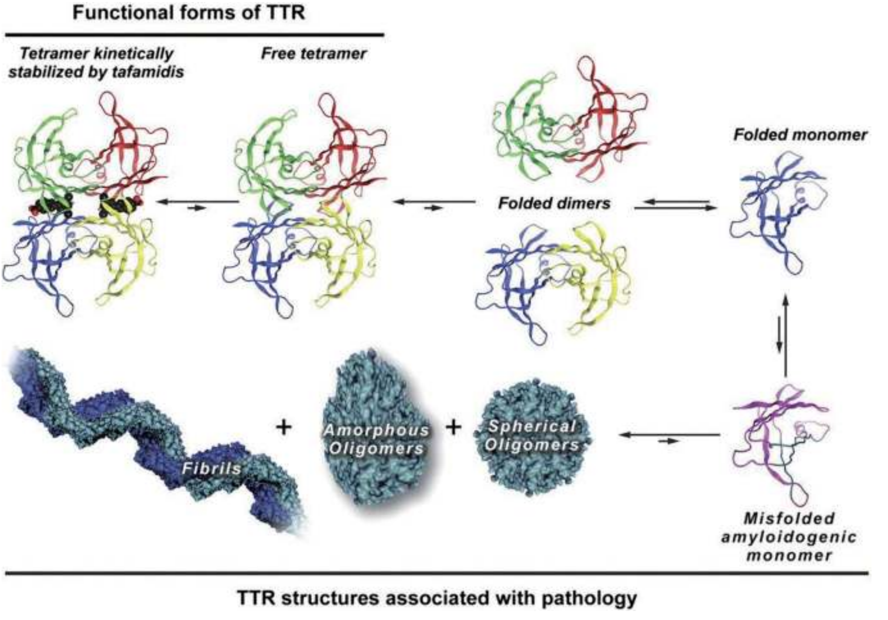


Figure 1.
Amyloid formation by TTR requires rate-limiting tetramer dissociation to a pair of folded dimers, which then quickly dissociate into folded monomers. Partial unfolding of the monomers yields the aggregation-prone amyloidogenic intermediate. The amyloidogenic intermediate can misassemble to 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

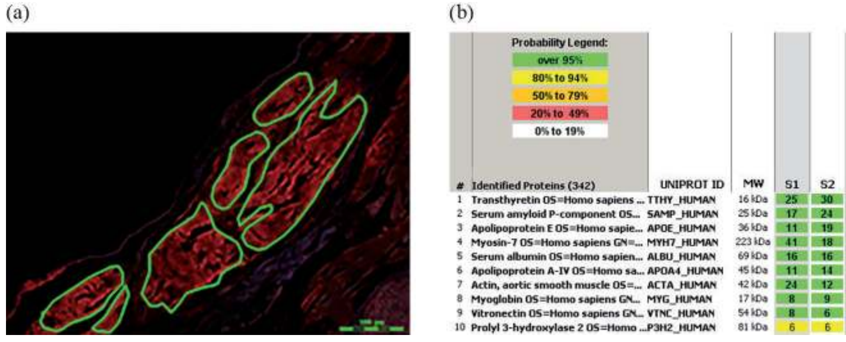
There is a marked variation in the prevalence and age of onset of ATTR in different countries, partly as a result of variation in the type of pathogenic mutation. fATTR is endemic in northern Portugal, Sweden and Japan, but sporadically occurs everywhere in the globe, with estimated number of about 5–10,000 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 he allele prevalence of 0.0173; i.e. 3.43% of African Americans carry at least one copy of the mutant gene [16]. Val122Ile related fATTR 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 fATTR. 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 a 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 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; 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 spectroscopy 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



#	Identified Proteins (342)	UNIPROT ID	MW	S1	S2
1	Transthyretin OS=Homo sapiens ...	TTHY_HUMAN	16 kDa	25	30
2	Serum amyloid P-component OS...	SAMP_HUMAN	25 kDa	17	24
3	Apolipoprotein E OS=Homo sapie...	APOE_HUMAN	36 kDa	11	19
4	Myosin-7 OS=Homo sapiens GN=...	MYH7_HUMAN	223 kDa	41	18
5	Serum albumin OS=Homo sapien...	ALBU_HUMAN	69 kDa	16	16
6	Apolipoprotein A-IV OS=Homo sa...	APOA4_HUMAN	45 kDa	11	14
7	Actin, aortic smooth muscle OS=...	ACTA_HUMAN	42 kDa	24	12
8	Myoglobin OS=Homo sapiens GN...	MYG_HUMAN	17 kDa	8	9
9	Vitronectin OS=Homo sapiens GN...	VTNC_HUMAN	54 kDa	8	6
10	Prolyl 3-hydroxylase 2 OS=Homo ...	P3H2_HUMAN	81 kDa	6	6

Figure 2.
Laser microdissection of amyloid deposits and mass spectroscopy. (a) Congo red-stained section of the postmortem heart specimen viewed under fluorescent light source. Bright red areas represent amyloid deposits. Areas microdissected for mass spectrometry-based proteomic analysis are indicated by purple-colored lines. (b) The results of mass spectrometry-based proteomics analysis of amyloid plaques obtained by microdissection. The identified proteins are listed according to the relative abundance they were represented in two independent microdissections. The top 10 proteins are shown. The columns show the protein name, the UnitProt identifier (protein accession number in the UniProt database, http://www.uniprot.org/), the molecular weight of the protein (MW) and two microdissections (S1-S2). The numbers indicate number of total peptide spectra identified for each protein. The most abundant protein is TTR. Apolipoprotein E, serum amyloid P-component and apolipoprotein A-IV are constituents of many amyloid types. In contrast, the peptides representing TTR (The top hit) are only seen in ATTR amyloidosis [from [91] with permission].

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.

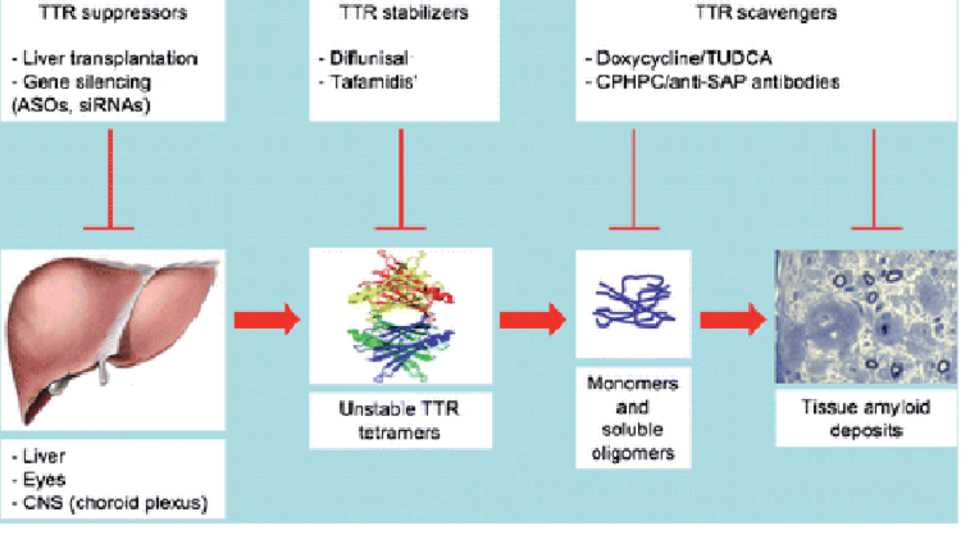


Figure 3.
Treatment strategies for fATTR (modified, from [92], with permission).

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 the 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-Val3 Met 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 100×10^9/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 did 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 evens 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 cardioembolic 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 loyalties 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 Rezania[1]* and Laleh Saadat[2]

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

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