Journal of Neurology (2018) 265:976–983
https://doi.org/10.1007/s00415-017-8708-4

NEUROLOGICAL UPDATE

Transthyretin familial amyloid polyneuropathy: an update

Violaine Plante-Bordeneuve[1]

Received: 29 November 2017 / Revised: 7 December 2017 / Accepted: 8 December 2017 / Published online: 16 December 2017

Abstract
Transthyretin familial amyloid polyneuropathy (TTR-FAP) is a progressive, fatal, inherited disorder first identified in Portugal and now recognized in all continents. Over the past decade, thanks to the availability of the genetic test, our knowledge on the range of clinical expressions of this disorder has expanded, including different patterns and progression rates of the neuropathy, as well as aspects of the cardiomyopathy, which can be prominent. In the mean time, new tools are being developed to detect earlier TTR amyloid deposition such as cardiac scintigraphy with technetium-labelled pyrophosphate tracers or small nerve fiber alterations from skin biopsies, or using neurophysiological approaches as well as magnetic resonance neurography (MRN). Such refinements, along with an increased awareness of the disease, should reduce the diagnostic delay and facilitate early treatment. In this regard, thanks to a better understanding of the TTR amyloid formation, major advances have been made, allowing for therapeutic developments which are less invasive than liver transplantation (LT). TTR stabilizer drugs are safe and seem to delay the disease progression in some groups of patients. Indeed, positive results have just been released from 2 phase III trials on TTR gene modifiers, namely silencing RNA and antisense oligonucleotide therapies. These recent advances open a new area in the field with the hope that we can safely bring about long-term stabilization of the disease. Furthermore, immunotherapies targeting the amyloid deposits are being explored.

Keywords Transthyretin amyloidosis · Neuropathy · Treatment · Genetic · Gene modifyers therapy

Abbreviations

ASO	Antisense oligonucleotides
ATTR	Transthyretin amyloidosis
mBMI	Modified body mass index
CSF	Cerebrospinal fluid
CPHPC	(R)-1-[6-[(R)-2-carboxy-pyrrolidin-1-yl]-6-oxo-hexa-noyl]pyrrolidine-2 carboxylic acid)]
CIDP	Chronic inflammatory demyelinating polyneuropathy
FAC	Familial amyloid cardiomyopathy
FAP	Familial amyloid polyneuropathy
IENFD	Intra-epidermal nerve fiber density
LT	Liver transplantation
mRNA	Messenger ribonucleic acid
MRN	Magnetic resonance neurography
NIS	Neuropathy Impairment Score
NIS-LL	Neuropathy Impairment Score in Lower Limbs
Norfolk QOL-DN	Norfolk quality of life Diabetic Neuropathy
NSAID	Non-steroidal anti-inflammatory drug
SAE	Serious adverse event
siRNAs	Small interfering RNAs
SAP	Serum amyloid P
TTR	Transthyretin

Introduction

Since the first description of the disease by *Corine Andrade* (1952) [1] in Portugal, our knowledge and management of TTR-FAP has changed in a number of ways and continues to do so. First, on the epidemiological front, the disorder that was once thought to be restricted to a small area of Northern Portugal is now recognized as a global disease, identified in all continents. A variety of phenotypes and mutations are known with more than 150 amyloidogenic TTR mutations identified and a range of clinical manifestations including much interest in cardiological aspects of the disease along

✉ Violaine Plante-Bordeneuve
violaine.plante@aphp.fr; vplante@free.fr

[1] Department of Neurology and Amyloid Network, University Hospital Henri Mondor, 51 Avenue du Maréchal de Lattre de Tassigny, 94000 Créteil, France

with CNS manifestations in patients with long-term survival [2]. In addition, differences in the natural history of the disease are observed. Refinement in imaging techniques now allows for the visualization of alterations in the peripheral nervous system by MRN and amyloid load in different organs using scintigraphy. However, identification of the amyloid type requires DNA testing and demonstration of amyloid deposits on a tissue biopsy [3], and in this respect, recent contributions from cutaneous nerve biopsy specimens have been helpful. In addition to these improvement in diagnosis, important advances have been made in the treatment of TTR-FAP [4]. Drugs like TTR stabilizers are safe and seem to delay progression of the disease in some groups of patients and of late new therapeutic developments are being pursued, including different gene therapy approaches. This review will cover the most recent diagnostic and therapeutic developments in the field.

Epidemiology/genetics

Significant advances have been made in the field due to the widespread availability of the genetic test. The genotype–phenotype spectrum of the disease is now better known. The ATTR-Val30Met is the commonest variant in Europe and Latin America, whereas the ATTR-Val122Ile predominates in USA. Approximately 4% of black Americans carry the ATTR Val122Ile substitution, previously associated with late-onset cardiomyopathy and increased mortality from heart failure, although this has not been confirmed in a longitudinal follow-up of a large cohort [5].

In China, as many as 20 different pathogenic TTR mutations have now been identified mainly in Han patients [6]. In Africa, the prevalence of the Val122Ile variant is the highest in the six countries of West Africa [7]. However, it is most likely that the disease remains underdiagnosed in many developing parts of the world.

Genetic modifiers of the phenotype

Several works have sought to unravel the genetic factors that might influence phenotypic expression and/or variability of age of onset as observed between and even within families. Such modifiers might be located either in the region next to the TTR gene, as suggested by recent haplotype association analyses [8, 9] or more distant through other gene interactions, as explored using candidate genes approaches [10, 11]. A first study on mRNA expression profiles on blood cells showed an expression pattern that differentiated ATTR-Val30Met patients from asymptomatic gene carriers with 80% accuracy [12]. In addition, in one study on a large cohort of ATTR-Val30Met carriers, mtDNA copy number was associated with earlier events and might be a modifier on age of onset [13].

New facets of the disease, natural course

The prevalence and extent of the cardiac aspect of the disease has been much better characterized in recent years, thanks to the relative ease of genetic testing and the development of new diagnostic tools [2]. Thus, in a prospective multi centre cross-sectional study performed in France, sequencing of the TTR gene showed that as many as 5% of patients diagnosed with hypertrophic cardiomyopathy have TTR related FAC [14].

In addition, a better understanding of the natural course of the disease has emerged along with the development of better clinical tools, particularly in the context of trialing new therapies. In a study comparing, systematically, 60 acquired amyloidosis patients and 41 with inherited TTR-FAP, the authors found that TTR-FAP cases had significant longer survival, higher composite autonomic severity scale scores, more frequent weakness, and delayed systemic involvement [15]. Some ATTR variants like Ile107Val and Thr60Ala are associated with a more severe and rapid course [16]. Indeed, French patients with the TTR-FAP genotypes Ile107Val, Ser77Tyr, and late-onset Val30Met show a more rapid and severe disease progression compared to Portuguese Val30Met patients, with onset of gait disorders three times faster. Median survival was also significantly shorter in Ile107Val and late-onset Val30Met patients [17].

The tools used to assess the progression of the neuropathy have been refined. The first trials on TTR stabilizers relied on clinical tests or composite scores previously tested in diabetic neuropathy. Their specificity and adequacy for TTR-FAP were initially assessed in a cross-sectional monocentric study in Portuguese Val30Met TTR-FAP patients and showed that the clinical NIS-LL and QOL-DN scores discriminated between disease stage and that mBMI declined progressively with disease stage. Overall, NIS-LL, NIS, Norfolk QOL-DN, and composite clinical and neurophysiological end points of nerve fiber function like the NIS+7, developed for the subsequent trials, appeared valid, and reliable measures of TTR-FAP severity [18, 19].

Pathology

Recent insights into our understanding of the pathogenesis of ATTR neuropathy came from an electron microscopic study of sural nerve biopsy specimens from 49 Val30Met patients (11 early and 38 late-onset cases) from Japan. This careful work suggests that direct insult of amyloid fibrils causes Schwann cell damage, resulting in the predominant

loss of small-fiber axons characteristic of early onset cases. Vasculopathy may also contribute to the pathogenesis of the neuropathy in late-onset cases [20]. In this setting, TTR-FAP has neither the pathology nor the clinical features of vasculitis neuropathy. Interestingly, damage to basal lamina, Scwann cells by amyloid fibrils have been mentioned in earlier reports on TTR-FAP.

Diagnostic challenges, "red flags", and misdiagnosis

The early diagnosis of an ATTR neuropathy is of paramount importance so as to allow for treatment with one of the therapeutic options. Diagnosis delay and misdiagnosis are still common because of phenotypic heterogeneity, late symptom onset, and lack of family history [3]. In a recent study from Italy, the rate of misdiagnosis was as high as 32% with an average delay of 46 months, from first symptoms to diagnosis. The most frequent diagnostic error is CIDP which occurs in about 20% of cases, followed by lumbosacral radiculopathy, lumbar canal stenosis, paraproteinaemic neuropathy, and AL amyloidosis. Such errors lead to inappropriate treatments such as immune therapy, chemotherapy, or spinal surgery in number of cases [21]. Sensory-motor deficits, areflexia along with demyelinating features on nerve conduction studies and increase CSF protein levels, are the main factors responsible for the misdiagnosis of CIDP. Notably, clinical and electrophysiological findings sometimes fulfill established criteria for CIDP (as defined by the European federation of Neurological society) in up to 37% of cases [17, 21]. Overall, a progression of the neurological deficit under different inappropriate treatment like intravenous immunoglobulin or corticosteroids should be the alarming feature leading to reconsider the diagnosis.

"Red-flag" symptoms have been reviewed using a literature data. Accordingly, TTR-FAP should be suspected if a progressive symmetric sensory-motor polyneuropathy is observed in combination with one or more of the following: family history of neuropathy, symptoms suggestive of autonomic dysfunction, cardiac involvement (i.e., hypertrophy, arrythmia, atrio-ventricular or ventricular blocks, and cardiomyopathy), gastrointestinal manifestations, inexplicable weight loss, bilateral carpal tunnel syndrome, renal impairment, and vitreous opacities [22, 23].

The pathology and TTR gene testing together are of crucial importance in making the diagnosis [3]. Notably, in the Italian work, even when an amyloid neuropathy was suspected, the absence of amyloid deposits on a tissue biopsy led to clinicians rejecting the diagnosis in 40% of cases, without gene testing [21]. In this respect, it is well recognized that the diagnostic sensitivity of biopsy varies greatly across tissues and at various stages of disease, all of which further emphasizes the need for centers of expertise to be called upon for the diagnosis.

New diagnostic tools

New diagnostic tools look set to allow for an earlier and more reliable diagnosis of this condition.

Magnetic resonance Neurography

Kollmer et al. [24] found increased nerve cross-sectional area in patients and asymptomatic gene carriers (AGC) at thigh level, but not distally suggesting predominant involvement of the proximal regions of the nerves at the early stages of the disease. Most recently, the same group found significant MRN signal differences in distal sural nerves between TTR-FAP patients, asymptomatic gene carriers, and controls. This outstanding work provides Class III evidence that MRN accurately identifies early peripheral nerve lesions in gene carriers. Although still exploratory, such approach might prove useful for early diagnosis [25].

Radionucleotide cardiac scintigraphy

It has long been recognized that technetium-labelled bone scintigraphy tracers can localize to myocardial amyloid deposits. Use of this imaging for the diagnosis of cardiac ATTR has now been revisited. A multicentre study on 1217 cases confirmed the diagnostic value of positive cardiac scintigraphy (grade 2 or 3 radiotracer uptake) by showing that a reliable diagnosis (100% positive predictive value) of cardiac ATTR could be made without the need for histology in patients who do not have monoclonal gammopathy. Accordingly, non-invasive diagnostic criteria were proposed, applicable to the majority of patients [26]. Such a technique is now a recognized approach for the diagnosis of ATTR cardiomyopathy.

Cutaneous nerve biopsy

The potential usefulness of skin biopsies in the assessment of the neuropathy associated with amyloid deposits has been investigated recently, with IENFD being tested as a potential biomarker of the disease [27, 28]. So far, its impact on patient management remains uncertain, because this test is not performed in most centers.

Other tools

Ultrasound B-mode images periumbilically have been used to screen amyloid deposits [29]. Feet electrochemical skin conductance is useful to detect early dysautonomia in

TTR-FAP [30]. However, its ability to track the disease longitudinally in terms of its autonomic neuropathy is still to be explored.

Treatment

Liver transplantation

LT was the first treatment option in TTR-FAP and has been used since 1990. It replaces the main source of mutant TTR through the production of wild-type TTR protein by the donor organ. In a 20-year retrospective analysis on 1940 patients collected across the world, the procedure was shown to increase survival especially in early onset (< 50 years-old) ATTR-Val30Met patients with a 15-year survival close to 80%. In contrast, the 10-year survival is below 50% in non-Val30Met and in older Val30Met patients. In addition, mBMI, early onset of disease (< 50 years of age), disease duration before LT, and ATTR-Val30Met mutations (versus ATTR-non-Val30Met) are independent survival factors [31, 32]. The procedure is obviously invasive with a significant morbidity and a 1-year mortality rate of 7–25%. Chronic renal failure and diabetes occur in approximately 20% of LT patients, and cardiovascular mortality (22% of deaths) is much higher than in patients undergoing LT for liver disease [31, 32]. Recent works reporting on the central nervous manifestations of this condition and its treatment reveal that there is moderate cognitive decline after LT in patients with disease duration above 10 years [33–35]. In a survey from Japan, cerebral amyloid angiopathy manifesting as transient focal neurologic episodes occurred in 11% of ATTR patients post LT, on average 16.8 years after onset of the disease. In addition, leptomeningeal and perivascular localization of ATTR amyloid fibrils has been observed in one autopsy case [34]. Thus, cerebral amyloid angiopathy due to leptomeningeal TTR amyloid infiltration is now a concern in patients with longer survival after LT.

TTR stabilizers

In ATTR, pathogenic mutations significantly destabilize the tetramer leading to its dissociation, in a rate-limiting step, into monomers, which in turn aggregate as amyloid fibrils. The concept of TTR stabilization as a therapeutic tool came from observations of late and mild phenotypes observed in compound heterozygote individuals Val30Met/Val119Met in whom there is much greater TTR tetrameric stability, due to a trans-suppressor effect of ATTR-Thr119Val [36]. In this context, oral TTR stabilizers were studied as treatments able to prevent amyloid deposition and slow disease progression. Tafamidis and diflunisal are 2 such stabilizers, binding to the TTR-thyroxine sites. Other TTR stabilizers like AG10 are also being developed and are in preclinical studies [37].

Diflunisal

Diflunisal, a non-steroidal anti-inflammatory drug (NSAID) developed in the 1970s, is a strong inhibitor of TTR amyloid fibril formation in vitro. It stabilizes TTR tetramers in healthy volunteers and FAP patients, at a dose of 250 mg twice daily [38]. A randomized multicentre, placebo-controlled phase 3 study confirmed that diflunisal slows the progression of the neuropathy in TTR-Val30Met and non-Val30met patients [39]. In addition, a single study reported a sustained effect of diflunisal on both neurological and cardiac functions in 14 patients treated for up to 48 months [40]. Diflunisal which has the designation of an orphan drug in ATTR is available worldwide and is inexpensive, although not currently accessible in all European countries. In the long term though, the safety concerns with NSAIDs are well known, and their contraindication in severe congestive heart failure and renal insufficiency may limit the use of diflunisal in a number of ATTR patients.

Tafamidis

Tafamidis (2-(3,5-dichloro-phenyl)-benzoxazole-6-carboxylic acid) kinetically stabilizes TTR in vitro, although the magnitude of its pharmacodynamic effect cannot be measured routinely [41]. The pivotal studies showed that Val30Met patients at a very early stage of their polyneuropathy (stage I), who were in receipt of Tafamidis 20 mg a day for 30 months, had a 56% greater preservation in neurological function, based on the NIS-LL than patients treated for 12 months [42, 43]. The findings suggested a higher efficacy of the drug at the earliest stage of TTR-FAP [43]. Tafamidis was approved in 2011 by the European Medicines Agency for the treatment of stage 1 TTR-FAP. It is currently available in Europe, Japan, and South America for the treatment of TTR-FAP, but has not been approved in the United States to date.

Delaying the progression of the neuropathy and a favourable safety profile in long-term treatment with tafamidis has been confirmed recently in Val30Met FAP patients [44, 45]. On the other hand, two studies from Italy and France reported less clear cut results. They provided data on the long-term follow-up in older Val30Met and non-Val30Met FAP patients treated with tafamidis 20 mg a day, on average for 24 months [46, 47]. Their results showed a significant functional progression of the neuropathy in 43 and 66% of the patients, respectively. Interestingly, at 36 months, the rate of responders to treatment, assessed by the NIS, was below 10% in the French study, whereas one-third of the patients did not show significant progression in the Italian

series. In both studies, BMI was preserved or significantly increased and the treatment well tolerated [46, 47].

The effect of the drug on TTR cardiomyopathy remains unelucidated. In one long-term study, 15% of patients showed cardiac disease progression and 30%, without cardiac involvement at baseline, developed a cardiomyopathy [46]. In this setting, an international multicentre placebo-controlled study is ongoing in hereditary and senile transthyretin amyloid cardiomyopathy [48].

Gene modifying therapy approaches

As TTR function seems dispensable in vivo, it is not expected that knocking-down *TTR* gene expression will lead to serious consequences in the long term. Two types of gene silencing therapies have been evaluated in phase 3 clinical trials: antisense oligonucleotides (ASOs) and small interfering RNAs (siRNAs). By strongly reducing both mutant and wild-type TTR plasma levels, it is hoped that such approaches will stop disease progression. Some reversal of established manifestations might also be observed in this context.

Antisense oligonucleotides

ASOs were developed targeting the 3′ untranslated region of the gene. Their potential to significantly decrease both the mutant and the wt TTR mRNA synthesis in the liver and the serum has been demonstrated in transgenic mouse models and in primate models [49]. In a phase 1 study, the leading ASO (Inotersen) was well tolerated in healthy volunteers and reduced the serum protein levels by 75% on average [50]. A 15-month double-blind, controlled phase 3 study has been conducted to evaluate the efficacy and safety of Inotersen in TTR-FAP. The study enrolled 172 patients across the world, with biopsy proven stage 1–2 familial TTR neuropathy and 27 different pathogenic TTR variants (53% ATTR-V30M). The results showed sustained reductions in TTR levels averaging 80% compared to baseline. Importantly, Inotersen met both primary endpoints compared to placebo with high levels of statistical differences. However, thrombocytopenia and renal dysfunction were key safety concerns using this agent. Weekly renal and platelet monitoring implemented right after these SAE were reported, as effective with no more related SAE having been observed. Over 95% of patients who completed the study participated in the open-label extension study [51].

Small interfering RNAs

siRNAs are small double-stranded RNAs that knock down a target mRNA in a sequence-specific manner by means of enzymatic degradation. For therapeutic use, siRNAs are delivered to the intra-cellular compartment of hepatocytes, thanks to their formulation with lipid nanoparticles [52]. An siRNA that targets the 3′ untranslated region of the *TTR* mRNA was developed and encapsulated into two different formulations of lipid nanoparticles ALN-TTR01 and ALN-TTR02 (Patisiran). The intravenous delivery of ALN-TTR01 and ALN-TTR02 (Patisiran) resulted in a knock down of hepatic *TTR* expression and reduced circulating levels of *TTR* by more than 80% in 32 TTR-FAP patients and healthy volunteers, respectively [53].

To evaluate the efficacy and safety of Patisiran in TTR-FAP, an 18-month double-blind, controlled phase 3 study has been conducted (the APOLLO trial). Patisiran 0.3 mg/kg was administered intravenously with oral dexamethasone premedication, every 3 weeks and randomized with placebo in a 2/1 ratio. The study enrolled 225 patients with TTR-FAP (76% males, 43% Val30Met), with a median age of 62y-o. Most recently, the results showed that Patisiran met the neurological primary end point using mNIS+7 and all secondary endpoints tested compared to placebo with extremely high levels of statistical significance. Moreover, a mean improvement in the mNIS+7 score from baseline, compared to placebo was reported across all subgroup analyses suggesting some improvement of the neuropathy. The safety profile of the drug was comparable to that of placebo [54].

Drugs targeting amyloid fibrils

In the last phase of TTR amyloid formation, the monomers are prone to misfold into soluble prefibrillar oligomers and then into insoluble TTR amyloid fibrils. Different experimental therapeutic approaches have tried to target specifically these late steps. Their goal is to clear amyloid deposits already in the tissue to reduce the amyloid load and ultimately to restore organ function. In this regard, anti-Serum Amyloid P (SAP) agents or anti-TTR antibodies are the main approaches now being developed.

Anti-serum amyloid P agents

This approach targets the serum amyloid P (SAP) component, a plasma protein found in all types of amyloidosis, that avidly but reversibly binds to tissue amyloid fibrils. The initial approach used the bis-D-proline compound CPHPC subcutaneously which forms complexes with circulating SAP that is cleared by the liver. After depletion of the circulating SAP using CPHPC, tissue bound SAP can then be targeted with monoclonal anti-SAP IgG antibodies to elicit complement dependent removal of the amyloid deposits by macrophages [55]. A phase 1 study tested this approach of a pre-treatment with CPHPC, followed by a single intravenous injection of a humanized monoclonal IgG1 anti-SAP antibody in patients with systemic

amyloidosis (mainly of the light-chain type). Four out of sixteen enrolled patients had a substantial reduction of their liver amyloid load as assessed ^{123}I SAP scintigraphy and hepatic magnetic resonance imaging [56]. A phase 2 trial is ongoing in patients with renal and cardiac amyloidosis including ATTR.

Anti-TTR antibody

Another potential treatment involves the use of TTR monoclonal antibodies that bind selectively to the monomers, non-native oligomers, and/or aggregates to prevent fibril formation or target them for removal by phagocytic mechanisms [57]. Recently, novel conformation-specific anti-TTR antibodies have been developed that target residues 89–97, within the F strand of TTR which are sequestered at the dimer interface of the tetramer. So far, 4 monoclonal antibodies have been identified that selectively bind to the target epitope on monomeric and non-native misfolded forms of TTR and strongly suppressed TTR fibril formation in vitro. These antibodies selectively bind aggregated ATTR, targeting it for phagocytic uptake by macrophages in heart tissue from patients [58]. Their clinical development is now being considered.

Genetic counselling and management of carriers

Once the diagnosis is confirmed in an index patient with the identification of a TTR pathogenic variant, predictive genetic testing can be offered to at risk relatives through genetic counselling. This process includes providing information on the genetic transmission, disease course, available therapeutics, as well as psychological support [22, 59]. When a carrier is detected, a baseline neurological and cardiac assessment along with structured follow-up is necessary to allow for the initiation of treatment at the earliest stage of disease. However, the transition from asymptomatic to symptomatic disease onset may be difficult to detect due to the heterogeneous manifestations of TTR-FAP, the lack of biomarkers, and possible negative biopsy findings. Clinical judgment is essential in this regard. In addition, the knowledge of the age-specific risk of disease (penetrance) is important for decision-making. Penetrance remains incomplete even up to the age of 80 y-o but varies between ATTR-Val30Met carriers in Sweden (69%) and in Portugal (95%). Penetrance profiles are being refined with significant differences identified with the 4 most frequent ATTR variants found in France [60]. Such an approach will allow for the better management of different mutation carriers.

Conclusion

Outstanding advances have been made in the knowledge of TTR-FAP in the last years increasing our ability to diagnose the disease. Importantly, a better understanding of TTR amyloid formation has allowed several therapeutic developments which are much less invasive than LT. Most recently, the positive results from the TTR gene modifiers trials open up a new era in the treatment of TTR-FAP. Our approach to treatment should, therefore, be revised accordingly with the ultimate goal being to stabilize and safely abrogate in the long term, disease progression in virtually all patients. In the future, the possibility to administrate combined anti-ATTR therapy has to be resolved so as to allow improvement in all the different organs affected in this condition.

Compliance with ethical standards

Conflicts of interest Support from Ionis, Alnylam, and Eidos therapeutics for participation to advisory boards.

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